# High-fat diet propels prostate cancer by rewiring the metabolome and amplifying the MYC program

**David P. Labbé[1,2,22,†],** Giorgia Zadra[3,4,†], Meng Yang[5], Jaime M. Reyes[1], Charles Y. Lin[6], Stefano Cacciatore[7], Ericka M. Ebot[8], Amanda L. Creech[9], Francesca Giunchi[10], Michelangelo Fiorentino[10], Habiba M. Elfandy[3], Sudeepa Syamala[3], Edward Karoly[11], Mohammed Alshalalfa[12], Nicholas Erho[12], Ashley Ross[13], Edward M. Schaeffer[14], Ewan A. Gibb[12], Mandeep Takhar[12], Robert B. Den[15], Jonathan Lehrer[12], R. Jeffrey Karnes[16], Stephen J. Freedland[17], Elai Davicioni[12], Daniel E. Spratt[18], Leigh Ellis[3,4,9], Jacob D. Jaffe[9], Anthony V. D'Amico[19], Philip W. Kantoff[1,20], James E. Bradner[1], Lorelei A. Mucci[8,21], Jorge E. Chavarro[5,8,21], Massimo Loda[3,4,9,*], Myles Brown[1,2,*]
[†]Co-first authors
[*]Co-corresponding authors

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, US
[2]Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, MA, US
[3]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, US
[4]Department of Pathology, Brigham and Women's Hospital, Boston, MA, US
[5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, US
[6]Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, TX, US
[7]Institute of Reproductive and Developmental Biology, Imperial College London, London, UK
[8]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US
[9]The Broad Institute of MIT and Harvard University, Cambridge, MA, US
[10]Pathology Service, Addarii Institute of Oncology, S-Orsola-Malpighi Hospital, Bologna, IT
[11]Metabolon, Morrisville, NC, US
[12]GenomeDx Biosciences, Vancouver, BC, Canada
[13]James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, Baltimore, MD, US
[14]Northwestern University Feinberg School of Medicine, Chicago, IL, US
[15]Department of Radiation Oncology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, US
[16]Department of Urology, Mayo Clinic Rochester, MN, US
[17]Department of Surgery, Division of Urology, Center for Integrated Research on Cancer and Lifestyle, Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, US and Surgery Section, Durham Veteran Affairs Medical Center, Durham, NC, US
[18]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, US
[19]Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US
[20]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, US
[21]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, US
[22]Present address: Division of Urology, Department of Surgery, McGill University and Research Institute of the McGill University Health Centre, Montréal, Québec, Canada

**Background:** Systemic metabolic alterations associated with increased consumption of saturated fat and obesity are linked with increased risk of prostate cancer progression and mortality but the molecular underpinnings of this association are poorly understood. Furthermore, the mechanisms by which metabolic rewiring alters the prostate cancer epigenome, the effector arm of intra- and extra-cellular signals, is equally nebulous.
**Methods:** We used the Hi-MYC prostate cancer mouse model for global metabolic and chromatin profiling, chromatin immunoprecipitation followed by sequencing (ChIP-seq) and transcriptomic analyses (RNA-seq). We also leveraged dietary intake and transcriptomic data from the Health Professional Follow-up Study (HPFS) and Physicians' Health Study (PHS) and clinicopathologic as well as genome-wide expression profiles from validation cohorts.

**Results:** Here, we demonstrate, in a murine prostate cancer model, that high-fat diet (HFD) enhances the MYC transcriptional program through metabolic alterations that favour histone H4K20 hypomethylation at the promoter regions of MYC regulated genes, leading to a HFD-dependent phenotype characterized by increased cellular proliferation and tumour burden. Importantly, these results are recapitulated in prostate cancer patients, where increased saturated fat intake (SFI), but not monounsaturated or polyunsaturated fat intake, is also associated with an enhanced MYC transcriptional signature. Additionally, the SFI-induced MYC signature independently predicts prostate cancer progression and death. Finally, a dietary intervention consisting of switching from a high-fat to control diet, greatly attenuates the MYC transcriptional program. **Conclusions:** Our findings suggest that in primary prostate cancer, dietary fat intake contributes to tumour progression by mimicking *MYC* over expression, setting the stage for therapeutic approaches involving changes to the diet.

**Conflict of Interest:** M.A., N.E., M.T., J.L., E.A.G. & E.D. are employees of GenomeDx Biosciences. E.K. is currently employed of Metabolon.

**Funding Acknowledgments:** D.P.L is a Lewis Katz – Young Investigator of the Prostate Cancer Foundation, and is the recipient of a Scholarship for the Next Generation of Scientists from the Cancer Research Society, and is also recipient of a Canadian Institute of Health Research Fellowship. G.Z. is a recipient of the Idea Development Award from the U.S. Department of Defense (DoD; PC150263) and the Barr Award from the Dana-Farber Cancer Institute. L.E., D.E.S. and L.A.M. are Young Investigators of the Prostate Cancer Foundation. Support for HPFS/PHS cohorts was provided by grants from the DoD (W81XWH-11-1-0529) and grants from the National Institute of Health (NIH; CA42182, CA58684, CA90598, CA141298, CA97193, CA34944, CA40360, CA131945, CA167552, P50CA090381, 1U54CA155626-01, P30DK046200, HL26490 and HL34595). The work reported here was supported by grants from the NIH (R01CA131945, R01CA187918 to M.L. and P50CA090381 to P.W.K., M.L. & M.B.), the National Cancer Institute (1P01CA163227 to M.B) and the Prostate Cancer Foundation to M.L. and M.B.