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Letter to the Editor

Revisiting 'what causes cancer?'

Susan Erdman.

Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Correspondence to: Villa JC, Department of Medical Oncology, General University of Ciudad Real, Spain; E-mail id: jvillaguzman1@yahoo.es;

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Letter to Editor

A thoughtful editorial previously published in *Cancer Studies and Therapeutics* pondered the question of "What is the Main Cause of Cancer?' [1]. Certainly there are no simple answers.

Perhaps a study by Poutahidis et al (2015) [2] provides some clues to this 'What Causes Cancer?' enigma. Their studies in animal models revealed multigenerational cancer phenomena that were transplantable using fecal microbiota alone. These findings raise the possibility that disrupted microbiota, arising from societal practices such as refined diets or antibiotics during earlier generations, may have carcinogenic consequences in subsequent generations. The authors postulated that detrimental microbial effects *in utero* and during infancy lead to a dysregulated host immune system featuring premature thymic involution, possibly via epigenetic mechanisms. Under these immune-suppressed conditions, future infant mucosal surfaces become more permeable to environmental threats including sepsis [3]. Extrapolating across generations, microbiota may function as part of a quorum sensing mechanism ultimately influencing host immune and hormonal homeostasis, thus altering cancer susceptibility of progeny animals [4]. In those studies, grandchildren of mice consuming 'fast food' diets were at high risk to develop cancer at a young age, even without other predisposing genetic or environmental risks.

These intriguing data are supported by other findings suggesting that bacteria should be on our 'What Causes Cancer?' radar screen [5-7]. Firstly, direct evidence exists in humans with *Helicobacter pylori* infection and inflammation-associated gastric cancer [8]. Likewise, in the lower bowel, infection with a related microbe *H. hepaticus* leads to inflammation-associated colon and mammary tumors in mice [9, 10]. Further, certain pathogenic *Escherichia coli* organisms are shown to cause DNA damage in gut epithelia [6], and even to invade the bloodstream and extra-intestinal tissues. Indeed, *E. coli* has been implicated in mastitis and breast cancer in women [11], whereas *Lactobacillus sp* apparently inhibits mammary cancer development [12]. This raises the possibility that certain microbiota serve as invisible mutagens or guardians that help to explain the enigma.

And there's more. Many studies have now shown that cancer-fighting capacity of our immune system can be mobilized or inhibited by our gut bacteria [10, 13-15]. Animal model systems mimicking complex cancer processes in human subjects reveal that microbes indirectly modulate tissue injury repair capacity and risk for tumor development and progression [3, 7, 9, 13-17]. For example, Poutahidis et al (2013) found that microbe therapy in mice led to proficient wound repair occurring twice-as-fast as in untreated controls [16]. Another study by Varian et al (2016) showed that microbe monotherapy was sufficient to increase thymus gland size, inhibit intestinal polyp formation, and increase lifespan in mouse models [18]. The proposed immune mechanisms involved microbial up-regulation of transcription factor Forkhead box protein N1 (FoxN1), the protein that is entirely lacking in athymic nude mice rendering them without T lymphocytes and as a result highly permissive to cancer growth [18, 19].

This leads us back to the original question of 'What causes Cancer?'. The original author posited that for a theory of to be widely accepted, the answer should explain the striking differences in cancer risk by age and among tissues [1]. We should at least consider the possibility that our modernized lifestyle practices using antibiotics, Caesarian births, and refined diets have depleted valuable diversity and beneficial organisms in our microbiome with carcinogenic consequences to future generations. After all, oral supplementation with a model organism *Lactobacillus reuteri*, once believed to be widespread in humans but now dwindling to <4% of people worldwide [4], was sufficient to rescue multigenerational health impairments in infant mice [2, 20].

Further research is needed to better understand the roles of microbiota among the many possibilities for "What is the Main Cause of Cancer?'. However, based on existing data, opportunities abound for engineering diets and microbe cocktails to reinforce host balance and extinguish cancer for generations to come.

References

1. López-Lázaro M (2016) What is the Main Cause of Cancer? *Can Stu The J* 1:1–2.
2. Poutahidis T, Varian BJ, Levkovich T, Lakritz JR, Mirabal S, et al. (2015) Dietary microbes modulate transgenerational cancer risk. *Cancer Res* 75: 1197–1204. [crossref]
3. Erdman SE, Poutahidis T (2015) Gut bacteria and cancer. *Biochim Biophys Acta* 1856: 86–90. [crossref]
4. Erdman SE, Poutahidis T (2016) Microbes and Oxytocin: Benefits for Host Physiology and Behavior. *Int Rev Neurobiol* 131: 91–126. [crossref]
5. Rao VP, Poutahidis T, Fox JG and Erdman SE (2007) Breast cancer: should gastrointestinal bacteria be on our radar screen? *Cancer Res* 67:847–850.
6. Arthur JC, Perez-Chanona E, Muhlbauer M, Tomkovich S, et al. (2012) Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 338:120–123.
7. Erdman SE (2016) Gut microbiota: Microbes offer engineering strategies to combat cancer. *Nat Rev Gastroenterol Hepatol* 13:125–126.
8. Wroblewski LE, Peek RM, Jr. and Wilson KT (2010) Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clinical microbiology reviews* 23:713–739.
9. Erdman SE, Poutahidis T, Tomczak M, Rogers AB, Cormier K, et al. (2003) CD4+ CD25+ regulatory T lymphocytes inhibit microbially induced colon cancer in Rag2-deficient mice. *Am J Pathol* 162: 691–702. [crossref]

10. Rao VP, Poutahidis T, Ge Z, Nambiar PR, et al. (2006) Innate immune inflammatory response against enteric bacteria Helicobacter hepaticus induces mammary adenocarcinoma in mice. *Cancer Res* 66:7395–7400.

11. Urbaniak C, Gloor GB, Brackstone M, Scott L, Tangney M, et al. (2016) The Microbiota of Breast Tissue and Its Association with Breast Cancer. *Appl Environ Microbiol* 82: 5039–5048. [crossref]

12. Lakritz JR, Poutahidis T, Levkovich T, Varian BJ, et al. (2014) Beneficial bacteria stimulate host immune cells to counteract dietary and genetic predisposition to mammary cancer in mice. *Int J Cancer* 135:529–540.

13. Erdman SE, Rao VP, Olipitz W, Taylor CL, Jackson EA, et al. (2010) Unifying roles for regulatory T cells and inflammation in cancer. *Int J Cancer* 126: 1651–1665. [crossref]

14. Vétizou M, Pitt JM, Daillère R, Lepage P2, Waldschmitt N3, et al. (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 350: 1079–1084. [crossref]

15. Sivan A, Corrales L, Hubert N, Williams JB, et al. (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science* 350:1084–1089.

16. Poutahidis T, Kearney SM, Levkovich T, Qi P, Varian BJ, et al. (2013) Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. *PLoS One* 8: e78898. [crossref]

17. Dvorak HF (2015) Tumors: wounds that do not heal-redux. *Cancer Immunol Res* 3: 1–11. [crossref]

18. Varian BJ, Goureshetti S, Poutahidis T, Lakritz JR, et al. (2016) Beneficial bacteria inhibit cachexia. *Oncotarget* 7: 11803–11816. [crossref]

19. Erdman SE (2016) Microbes and healthful longevity. *Aging (Albany NY)* 8: 839–840. [crossref]

20. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, et al. (2016) Microbial Reconstitution Reverses Maternal Diet-Induced Social and Synaptic Deficits in Offspring. *Cell* 165:1762–1775.

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