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1. List of changes edited in manuscript postcodes were added.

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2. Phone number was corrected +972-8- 934-4014 (phone)

Key word were added:

Key words: microbiome; non-gastrointestinal cancers; carcinogenesis; dysbiosis; microbial agent;

Core tip:

"The forgotten organ", the human microbiome, comprises a community of microorganisms that colonizes various sites of the human body. A complex host-microbiome relationship has emerged in which many functions became codependent. This coupling becomes evident when disruption in the microbiome composition, termed dysbiosis, is mirrored by the development of pathologies in the host. Among the most serious consequences of dysbiosis, is the development of cancer. As many as 20% of total cancers worldwide are caused by a microbial agent. Here, we will review the available evidence implicating microbiome involvement in the development and progression of non-gastrointestinal cancers. Developing a system-wide approach to cancer-microbiome studies will be crucial in understanding how microbiome influences carcinogenesis, and may enable to employ microbiome-targeting approaches as part of cancer treatment.

3. Citation was added [1]

4. [Summarized in table-1] was added to page 5 12 rows from above. The table should appear just before the **Conclusions and summary section.**

5. Reference format was corrected.

6. We had changed a few paragraphs in the text.

The paragraphs are heighted and listed here:

a. Page 5, 5th line from top - In this context, Toll-Like Receptor (TLR) 5 and its ligand flagellin linked between chronic inflammation, tissue damage and skin cancer. In the model described, bone-marrow (BM) chimeras lacking MyD88 and TLR5 in the hematopoietic cells exhibited protection against a chemical model of wound-induced tumor formation.

b. Page 5, 7th line from bottom – Breast cancer is the second leading cause of cancer–related deaths in women: one in eight women develop the malignancy in their lifetime[[28]. Despite considerable and significant progress has been achieved in breast cancer research, in most cases it's etiology remains unknown[[29]. Mammary glands are colonized by a distinct microbiota [30, 31], but the role of microbial involvement in breast cancer remains at its infancy.

c. Page 5, 12th line from top - The vagina harbors a unique microbiota that serves as an important line of defense against pathogens, including sexually transmitted infections (STIs) [55]. The dominant members of the vaginal microbiome *Lactobacillus spp*. were shown to provide broad-spectrum protection from pathogens through their production of lactic acid [56], bacteriocins (bactericidal proteinaceous molecules) [57], antagonistic bacteriocin- like substances [58], and biosurfactants [59], that can adhere to mucus, a component of the barriers against pathogens [60] and disrupt biofilms [61]. Disruption of the protective microbiota configuration, termed bacterial vaginosis (BV) was shown in numerous studies to correlate with cervical cancer–inducing HPV infections [62-69]. BV affects one in three U.S. women [70] and is characterized by decrease in protective *Lactobacillus spp*., increased specie richness, and elevated numbers of anaerobic bacteria, including species of *Gardnerella, Prevotella,* and *Clostridiales* [71].While numerous association studies showed a strong association between dysbiotic disruption of vaginal microbiota (BV) and HPV

infections, the mechanistic link between the two events is yet to be explored.

d. Page 14, 8th line from top - *C. pneumoniae* is a gram-negative obligatory intracellular bacterium and a common cause of pneumonia [69]. C. pneumoniae can also cause other conditions, such as sinusitis, bronchitis, rhinitis and worsening of chronic obstructive pulmonary disease (COPD). However, infection can also be asymptomatic. The involvment of *C. pneumoniae* infection in lung cancer development and risk has been suggested by several studies [97-99]. However, the mechanisms for this association remain unclear [101, 102].Pulmonary infections with gram-negative bacteria have also been suggested to contribute to lung metastasis. Acute lung infection models induced by either infection with *E. Coli* or administration of LPS increased cancer cell homing to the lung and enhanced lung metastasis [100]. Moreover, the broncho-alveolar lavage fluid from LPS- or *E. Coli*-injected mice induced the migration of transformed cells in vivo. The tumor cells migratory activity was blocked by AMD3100, a chemokine receptor-4 inhibitor, as well as by amoxicillin, an antibacterial agent. In addition, tracking of the metastatic tumor cell line in the mouse showed that bacteria injection enhanced early localization of the tumor cells to the lung.

e. Page 19, 4th line from top Non-alcoholic fatty liver disease (NAFLD), a component of the 'metabolic sydrome', is rapidly becoming a common cause of chronic liver disease in both developed and developing countries. [122].