site in various gene therapy protocols [11]. Genetic approaches include delivering genes encoding pro-drug activating enzymes, cytotoxic anti-angiogenic proteins, or cell-targeted toxins to the tumor. However Current gene therapy protocols require local administration of vectors. Therefore, a systemic delivery system is required that will allow therapies to be carried to both primary and metastatic tumors. As a result, bacteria and their products have been investigated as DNA delivery vectors, cell-targeted toxins, and tumor targeting vehicles. Bacteria Such as Salmonella typhimurium A1-R, Clostridium perfringens have been used as cell-targeted toxins and *Listeria monocytogenes* [12], *Shigella flexneri* [13], Lactococcus lactis have been shown to deliver a DNA expression plasmid and cDNA encoding a human cystic fibrosis transmembrane intracellular conductance regulator into mammalian cells, respectively. A genetically modified strain of L. lactis with a synthetic human IL-10 gene represents a promising treatment for inflammatory bowel disease [14]. Toxoplasma gondii is an obligate parasite. Infection of toxoplasma controls several cellular communication pathways to establish an antiapoptotic environment and decimate immune cells as a conduit for the dissemination. Although, high degree of ambiguity in the molecular mechanism of *T. gondii* dissemination through the host [15].

Helicobacter pylori and stomach cancer

Helicobacter pylori is a Gram-negative pathogen and have a unique ability to colonize the mucosal lining of the human stomach. This bacterium shows urease, catalase, and oxidase activity, it is spiral shape and possesses 3 to 5 flagella that are used for motility. *H. pylori* has evolved the ability to colonize the highly acidic environment found within the stomach by metabolizing urea to ammonia via urease, which generates an neutral environment enveloping the bacterium [16]. Helicobacter is a very important pathogen in the development of cellular gastric carcinoma, the growth of stomach cancer differs in different regions. Though anti- *H. pylori* treatments have been shown to be successful in preventing stomach cancer, the risk of this type of cancer initiated by *H. pylori* would be significantly decreased. *H. pylori* infection may be acquired during childhood, persists lifelong if not eradicated, and is associated with chronic gastritis and an increased risk of peptic ulcer disease and further gastric cancer [17]. Although, *H. pylori* colonization does not cause any symptoms in most persons [18]. *H. pylori* has several pathogenicity factors such as OipA, BabA, VacA, CagA, which are connected to the gastric epithelial cells by the receptor molecules on their surface, and this interaction creates a series of intracellular signaling cascade pathways, causing cell changes and ultimately damage to the cell such as CagA phosphorylation-dependent host cell signaling, CagA phosphorylation-independent host cell signaling, etc. [19]. CagPAI (The cag pathogenicity island (*cag* PAI) is a 40-kb DNA insertion element which contains 27 to 31 genes flanked by 31-bp direct repeats and encodes one of the most intensely investigated *H. pylori* proteins, CagA), VacA, Paptitoglycan, BabA, DupA, SabA, FlaA that are the virulence factors of the *helicobacter pylori* [20]. OipA is an inflammation-related protein. *H. pylori* contains either a functional or non-functional OipA gene and the functional OipA gene is significantly related associated with the presence of duodenal ulcers, gastric cancer, and increased neutrophil inflammation [21,22]. DupA increases Interleukin-8 production and it expresses the OipA gene of the *H. pylori* [23,24]. The chance of gastric carcinoma is induced not only by *H. pylori* strain and genetic makeup of the host cell but also by the environmental factors, high dietary salt intake of them can able to increase the risk of gastric cancer with the association of *H. pylori* [25,26]. A subsequent study on a Japanese population and a case-control study in South Korea each give an account that *H. pylori*-infected subjects consuming a high-salt diet had an increased risk of gastric cancer compared to *H. pylori*-infected subjects who consumed lower levels of salt [27,28], while another study reported a positive correlation between the prevalence of *H. pylori* infection and levels of dietary salt intake [29]. The result of this study indicated that many factors are involved in virulence and *H. pylori* is capable to cause peptic ulcers as well as gastric cancer.

Papilloma virus and cervical cell carcinoma

Papillomavirus is a tiny, epitheliotropic, non-enveloped, double-stranded DNA virus that infects cutaneous and mucosal epithelia in a species-specific manner except bovine papillomavirus (BPV_s) 1 and 2 are known to infect Mesenchymal tissues and to show inter species transmission. More than 100 types of Human papillomaviruses have been identified and half of them cause infection in the urogenital tract [30]. According to WHO statistics, high-risk HPV DNA is found to be present in 99.7% of cervical cancer specimens [31]. HPV infection types are divided into two groups based on their carcinogenic properties: these are high risk and low risk. High-risk type (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, and 59), Others are classified as potential high risk

(which are 53,56,70,73, and 78). HPV16 and HPV18, it has been proven that both of strains are most virulent and high-risk human papillomavirus [32]. The available literature indicates that there are two discrete intraepithelial processes in the cervix associated with human papillomavirus. One is the classical condyloma. The other is intraepithelial neoplasia, like classical infection, which may be mature [cervical intraepithelial neoplasia (CIN) with koilocytosis] or immature (high-grade CIN or carcinoma in situ). HPV16 and HPV18 are the only existing HPV types With DNA that can integrate their DNA with the host cell [33]. Many studies have been confirmed that persistent infection with an oncogenic HPV type, mainly 16 and 18 is the main risk factor for the development of cervical intraepithelial neoplasia (CIN) that may range from CIN1 to CIN3 and cancer [34]. Oncogenic ability of HPV16 depends on the regulation of viral transcriptional factors. At the initiation of viral infection, the HPV16 genome can be presented as an unintegrated small DNA molecule also called episome, and results in benign and precancerous lesions of the cervix. However, HPV16 can integrate its genome into the host genome, which in turn can lead to the development of cervical carcinoma and cervical intraepithelial neoplasia grade III [35]. E6 is an envelope protein, that binds with E6-associated binding protein (E6AP), a ubiquitin ligase leading to a structural change in E6 allowing it to bind with p53(guardian of the genome), the cell cycle control tumor suppressor protein to form a trimeric complex E6/E6AP/p53. This binding leads to the degradation of P53 and the result is cell proliferation. On the other hand, E7 binds with pRb causing its degradation and inactivation [36]. At normal physiology of the cell, pRb downregulates E2F a transcription factor. As pRb is deactivated by E7, E2F is upregulated and cell proliferation genes are activated, furthermore, E6 and E7 have been shown to form complexes with hundreds of other proteins in the host cell [37,38]. However subsequent study shows that E6/E7 deregulates the mi RNA linked to carcinogenesis [39]. miRNA plays an important role in the posttranscriptional control of the expression of host genes. Many recent studies proposed that E7, E6, and E5 oncoproteins regulate the host mi-RNA profile. In HPV-associated cervical cancer cells, a number of miRNAs such as miR-21, miR-143, and miR-9 are overexpressed, thus targeting CCL20 (chemokine (C-C) motif ligand) and promoting the migration of HPV16-positive cancerous cells. However, overexpression of some miRNAs such as miR-203 inhibits HPV amplification (Figure 1). Thus miR-203 is suppressed by the overexpression of HPV E7 [40].

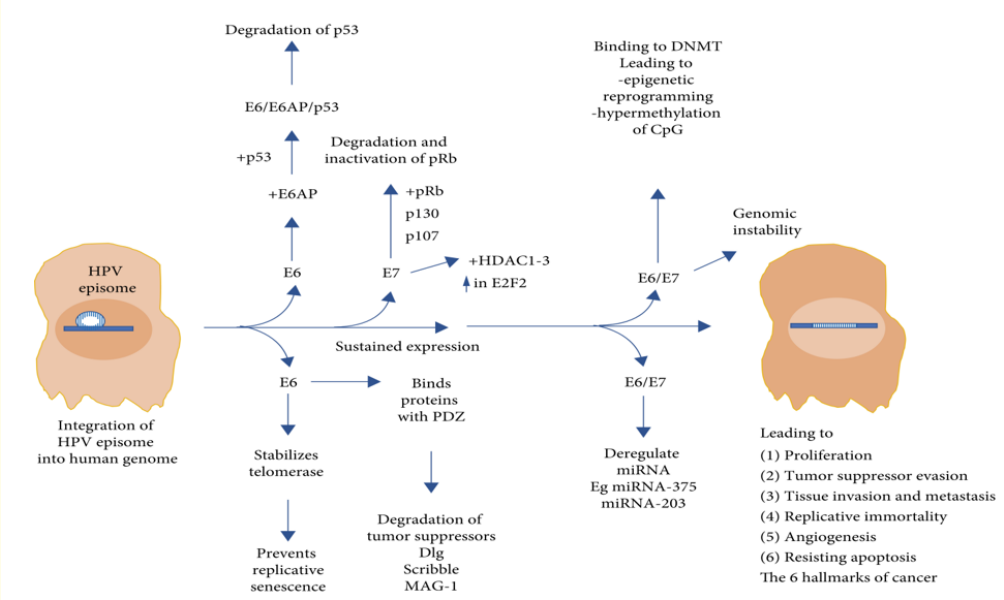

Figure 1: Progression of cervical carcinogenesis, Which involves HPV gene integration leads to the degradation of P53 and inactivation of pRb, mi-RNA by the binding of E6 and E7 viral protein tends to the uncontrolled cellular proliferation, tumor suppression evasion, and other feature of tumorigenicity [41].

Epstein-Barr virus and Burkitt's lymphoma

Epstein-Barr virus(EBV) is the first human virus that is proved to be carcinogenic. a double-stranded linear DNA genome and is enclosed by capsid proteins [42]. Primarily EBV is found associated with Burkitt's lymphoma, but now we have a lot of evidence that EBV is linked to a remarkably wide range of lymphoproliferative lesions and malignant lymphomas of B-, T- and NK-cell origin. Latent infection of EBV express a variety of genes which includes, six EBV nuclear antigens such as EBNA-1, -2, -3A, -3B, -3C, and EBV nuclear antigen-leader protein(EBNA-LP), three EBV latent membrane proteins such as LMP-1, -2A, and -2B, two short non-coding RNAs like EBV-encoded small RNA, EBER-1 and -2 [43,44]. EBV can infect various cell types, so human EBV_s infection leads to the development of various cancers. Due to the preferential infection of B cells, the most common forms of EBV-associated lymphoproliferative disorders are B-cell lymphomas. Some epidemiological studies show that the Epstein-Barr virus is restricted to the geographical region where Plasmodium falciparum malaria is holoendemic [45]. This virus is potentially able to infect epithelial cells as well as B cells [46]. Burkitt's lymphoma and Epstein-Barr virus have a strong relation in the immuno-compromised person [47]. Epstein-Barr virus related to Burkitt's lymphoma according to its epidemiologic and clinical characteristics is classified into three groups including HIV associated Burkitt's lymphoma, endemic Burkitt's lymphoma, and sporadic Burkitt's lymphoma. Endemic Burkitt's lymphoma engages the jaw and facial bones and sporadic Burkitt's lymphoma engages the upper respiratory tract and intestines, both leading to tumors in those areas [48]. The last two decades of Studies show that the interactions between the virus and B cells prepare the ground for the development of Burkitt's lymphoma and the key factor in tumorogenic of Burkitt's lymphoma is the activation of C-myc (C-myc is a proto-oncogene may convert into oncogene which encodes a nuclear phosphoprotein that plays a Crucial in cell cycle progression, apoptosis, and cellular transformation) oncogene through its transfer into the immunoglobulin region.

Streptococcus bovis and Colorectal cancer

Streptococcus bovis is currently named *Streptococcus gallolyticus.* As the third most common malignancy and the second most deadly cancer, colorectal cancer (CRC) induces an estimated 0.9 million deaths and 1.9 million new cases were reported worldwide in 2020. The incidence of CRC is higher in highly developed countries, and it is increasing in middle and low-income countries due to western food habits [49-51]. *S. gallolyticus is mainly associated with colonic neoplasia and extracolonic malignancy. However, all genospecies are not closely related to the CRC.* A study conducted by Tsai., *et al*. in 2016 showed that between 25 and 80% of patients with *S. bovis* bacteremia have concomitant colorectal tumors. In this study, a total of 107 patients with *S. bovis* bacteremia were identified and investigated with colonoscopy, 15 of these patients (30.6%) had colorectal adenocarcinoma [52]. *Another study conducted by* Jason S. Gold., *et al.* in 2004 showed that Forty-five patients (41 adults, 4 children) with documented *S. bovis* bacteremia during 12 years were identified, and 17 (41%, adults) out of 45 underwent colonoscopy. Colonic neoplasia was present in 16 patients (39% of adults), with 3 of these patients having invasive colorectal cancer (7% of adults). Invasive cancer was present in 13 patients (32% of adults). Eight patients had malignant lesions arising within the gastrointestinal tract, and 5 patients had extraintestinal malignancies. All the data related to *S. bovis* bacteremia conclude that it is associated with colonic neoplasia and extracolonic malignancy.

Discussion

The Microbial aspect of the cancer plays an important role in inducing cancer as various microorganisms affect different mechanisms of the body to induce malignancy in cells. The type of microorganisms being listed in the above review article shows that how different types of microorganisms alter gene mechanisms, make fool out of the immune system, alterations in signaling pathways, increased the rate of growth signal inhibitors, and many such factors. However, another area of research interest that can be of great importance is the therapeutic aspect of microorganisms towards the cure of cancer as the healing mechanisms of cancer would be inward driven resulting in the cure of cancer while causing no harm to the human body as the treatment used in present scenario have side-effects and are not reversible. So microbial aspects of cancer hold great potential in both diagnosis and treatment.

Conclusion

In recent times the advancements are such that cancer can be diagnosed and treated as well. However microbial agents play an equally important for research, some of the deeper research is

required in order to get a better understanding of the microbial aspect of cancer because microbe and other microbial flora hold the potential to induce cancer, and modify body cells, genetic mechanisms, body environments. These are the small key factors that also play an important role in cancer to get induced. Another important key factor is the effect of microbes on the body and how the makeup of the body cell gets changed. Another aspect of research can be the therapeutic aspect of microbes towards cancer as the treatment used today such as chemotherapy, cyto proteins, they may be cytotoxic and the changes it does to the body are non-reversible further research towards this aspect via advanced biotechnological approach and microbiological practices would make advancements further.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Bibliography

1. Zur Hausen H. "Infections Causing Human Cancer". Wiley-VCH, Weinheim-New York (2006): 1-517.
2. Feng Huichen., *et al*. "Clonal integration of a polyomavirus in human Merkel cell carcinoma". *Science (New York, N.Y.)* 319.5866 (2008): 1096-1100.
3. Wroblewski Lydia E.., *et al*. "*Helicobacter pylori* and gastric cancer: factors that modulate disease risk". *Clinical Microbiology Reviews* 23.4 (2010): 713-739.
4. van Tong Hoang., *et al*. "Parasite Infection, Carcinogenesis and Human Malignancy". *EBioMedicine* 15 (2017): 12-23.
5. Zhijian Gao., *et al.* "Use of Clostridium perfringens enterotoxin and enterotoxin receptor-binding domain (C-CPE) for cancer treatment: opportunities and challenges". *Journal of Toxicology* 2012 (2012): 9.
6. Jain N., *et al*. "Cancer Scenario in India". *Journal of Genetics and Genomic Sciences* 4 (2019): 014.
7. Mehrotra., *et al*. "Breast cancer in India: Present scenario and the challenges ahead". *World Journal of Clinical Oncology* 13.3 (2022): 209-218.
8. Menati Rashno., *et al*. "Microbiome in human cancers". *Access Microbiology* 3.8 (2021).
9. Zur Hausen Harald. "The search for infectious causes of human cancers: where and why". *Virology* 392.1 (2009): 1-10.
10. Misra Vatsala., *et al*. "*Helicobacter pylori* and gastric cancer: Indian enigma". *World Journal of Gastroenterology* 20.6 (2014): 1503-1509.
11. Jack A Roth., *et al.* "Gene Therapy for Cancer: What Have We Done and Where Are We Going?". *Journal of the National Cancer Institute* 89.1 (1997): 21-39.
12. Krusch Stefan., *et al*. "Listeria monocytogenes mediated CFTR transgene transfer to mammalian cells". *The Journal of Gene Medicine* 4.6 (2002): 655-667.
13. Sizemore D R., *et al*. "Attenuated Shigella as a DNA delivery vehicle for DNA-mediated immunization". *Science (New York, N.Y.)* 270.5234 (1995): 299-302.
14. Steidler Lothar.., *et al*. "Biological containment of genetically modified Lactococcus lactis for intestinal delivery of human interleukin 10". *Nature Biotechnology* 21.7 (2003): 785-789.
15. Laliberté J and V B Carruthers. "Host cell manipulation by the human pathogen Toxoplasma gondii". *Cellular and Molecular Life Sciences* 65.12 (2008): 1900-1915.
16. Vaux D L and A Strasser. "The molecular biology of apoptosis". *Proceedings of the National Academy of Sciences of the United States of America* 93.6 (1996): 2239-2244.
17. Ferlay Jacques., *et al*. "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012". *International Journal of Cancer* 136.5 (2015): 359-386.
18. Peek Richard M Jr and Martin J Blaser. "*Helicobacter pylori* and gastrointestinal tract adenocarcinomas". *Nature Reviews Cancer* 2.1 (2002): 28-37.
19. Soleimani N. "The Role of *Helicobacter pylori* in Gastric Cancer and its Clinical Applications in Cancer Treatment". *Journal of Mazandaran University of Medical Sciences* 27.147 (2017): 225-238.
20. Wroblewski Lydia E., *et al*. "*Helicobacter pylori* and gastric cancer: factors that modulate disease risk". *Clinical Microbiology Reviews* 23.4 (2010): 713-739.
21. Franco Aime T., *et al*. "Regulation of gastric carcinogenesis by *Helicobacter pylori* virulence factors". *Cancer Research* 68.2 (2008): 379-387.
22. Yamaoka Y., *et al*. "*Helicobacter pylori* outer membrane proteins and gastroduodenal disease". *Gut* 55.6 (2006): 775-781.

23. Lu Hong., *et al*. "Duodenal ulcer promoting gene of *Helicobacter pylori*". *Gastroenterology* 128.4 (2005): 833-848.

24. Yamaoka Yoshio., *et al*. "Role of interferon-stimulated responsive element-like element in interleukin-8 promoter in *Helicobacter pylori* infection". *Gastroenterology* 126.4 (2004): 1030-1043.

25. Correa P. "Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention". *Cancer Research* 52.24 (1992): 6735-6740.

26. Fuchs C Sand R J Mayer. "Gastric carcinoma". *The New England Journal of Medicine* 333.1 (1995): 32-41.

27. Shikata Kentaro., *et al*. "A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study". *International Journal of Cancer* 119.1 (2006): 196-201.

28. Lee Sang-Ah., *et al*. "Effect of diet and *Helicobacter pylori* infection to the risk of early gastric cancer". *Journal of Epidemiology* 13.3 (2003): 162-168.

29. Beevers D Gareth., *et al*. "Salt intake and *Helicobacter pylori* infection". *Journal of Hypertension* 22.8 (2004): 1475-1477.

30. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human Papillomaviruses. Lyon (FR): International Agency for Research on Cancer; 2007. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 90.) (2007).

31. Walboomers J M., *et al*. "Human papillomavirus is a necessary cause of invasive cervical cancer worldwide". *The Journal of Pathology* 189.1 (1999): 12-19.

32. Reid R., *et al.* "Genital warts and cervical cancer. I. Evidence of an association between subclinical papillomavirus infection and cervical malignancy". *Cancer* 50.2 (1982): 377-387.

33. Syrjänen K J and S M Syrjänen. "Human papilloma virus (HPV) infections related to cervical intraepithelial neoplasia (CIN) and squamous cell carcinoma of the uterine cervix". *Annals of Clinical Research* 17.2 (1985): 45-56.

34. Stanley M. "Pathology and Epidemiology of HPV Infection in Females". *Gynecologic Oncology* 117.2 (2010): 5-10.

35. Lehoux Michaël., *et al*. "Molecular mechanisms of human papillomavirus-induced carcinogenesis". *Public Health Genomics* 12.5-6 (2009): 268-280.

36. B Zhang., *et al*. "The E7 proteins of low- and high-risk human papillomaviruses share the ability to target the pRB family member p130 for degradation". *Proceedings of the National Academy of Sciences* 103.2 (2006): 437-442.

37. White Elizabeth A., *et al*. "Comprehensive analysis of host cellular interactions with human papillomavirus E6 proteins identifies new E6 binding partners and reflects viral diversity". *Journal of Virology* 86.24 (2012): 13174-13186.

38. Schiffman Mark., *et al*. "Carcinogenic human papillomavirus infection". *Nature Reviews Disease Primers* 2.1 (2016): 16086.

39. Hjung HM., *et al*. "miR-375 activates p21 and suppresses telomerase activity by coordinately regulating HPV E6/E7, E6AP, CIP2A, and 14-3-3ζ". *Molecular Cancer* 13.1 (2014): 80.

40. J Groves and N Coleman. "Pathogenesis of human papillomavirus-associated mucosal disease". *The Journal of Pathology* 235.4 (2015): 527-538.

41. Chee KC., *et al*. "Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination—Review of Current Perspectives", *Journal of Oncology* (2019): 11.

42. Grywalska Ewelina., *et al*. "Epstein-Barr virus-associated lymphoproliferative disorders". *Postepy Higieny I Medycyny Doswiadczalnej (Online)* 67 (2013): 481-490.

43. Middeldorp Jaap M., *et al*. "Pathogenic roles for Epstein-Barr virus (EBV) gene products in EBV-associated proliferative disorders". *Critical Reviews in Oncology/Hematology* 45.1 (2003): 1-36.

44. Thompson., *et al*. "Epstein-Barr virus and cancer". *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 10.3 (2004): 803-821.

45. Moormann., *et al.* "Malaria - how this parasitic infection aids and abets EBV-associated Burkitt lymphomagenesis". *Current Opinion in Virology* 20 (2016): 78-84.

46. Nilsson K. "Human B-lymphoid cell lines". *Human cell* 5.1 (1992): 25-41.

47. "IARC monographs on the evaluation of carcinogenic risks to humans/World Health Organization". *International Agency for Research on Cancer* 70 (1997): 1-492.

48. Wright D H. "What is Burkitt's lymphoma and when is it endemic?". *Blood* 93.2 (1999): 758.

49. Keum., *et al*. "Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies". *Nature Reviews. Gastroenterology and Hepatology* 16.12 (2019): 713-732.

50. Murphy, Neil., *et al*. "Lifestyle and dietary environmental factors in colorectal cancer susceptibility". *Molecular Aspects of Medicine* 69 (2019): 2-9.

51. Campos FG. "Colorectal cancer in young adults: A difficult challenge". *World Journal of Gastroenterology* 23.28 (2017): 5041-5044.

52. Tsai Cheng-En., *et al*. "Associated factors in Streptococcus bovis bacteremia and colorectal cancer". *The Kaohsiung Journal of Medical Sciences* 32.4 (2016): 196-200.

53. Parkin DM. "International variation". *Oncogene* 23 (2004): 6329-6340.

54. Uemura, N., *et al*. "*Helicobacter pylori* infection and the development of gastric cancer". *The New England Journal of Medicine* 345.11 (2001): 784-789.

55. Umeda Mayumi., *et al*. "*Helicobacter pylori* CagA causes mitotic impairment and induces chromosomal instability". *The Journal of Biological Chemistry* 284.33 (2009): 22166-22172.

56. Basso Daniela., *et al*. "Clinical relevance of *Helicobacter pylori* cagA and vacA gene polymorphisms". *Gastroenterology* 135.1 (2008): 91-99.

57. Moody Cary. "Mechanisms by which HPV Induces a Replication Competent Environment in Differentiating Keratinocytes". *Viruses* 9.9 (2017): 261.

58. Straight SW., *et al*. "The E5 oncoprotein of human papillomavirus type 16 inhibits the acidification of endosomes in human keratinocytes". *Viruses* 69.5 (1995): 3185-3192.

59. BURDETTE, W J. "The significance of mutation in relation to the origin of tumors: a review". *Cancer Research* 15.4 (1955): 201-26

60. Gold JS., *et al*. "Association of Streptococcus bovis Bacteremia With Colonic Neoplasia and Extracolonic Malignancy". *Archives of Surgery* 139.7 (2004): 760-765.