Review Article

The potential role of microbes in oncogenesis with particular emphasis on oral cancer

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ABSTRACT

لأكثر من قرن مضى كانت للأحياء الدقيقة (غير الفيروسية) وخاصة البكتيريا دور بارز كعامل مسبب للأورام السرطانية. وقدم عدد قليل من الباحثين عدة أدله تدعم نظرية (الجرثومة المسرطنة). وبإستثناء الرابط بين بكتيريا (*Helicobacter pylori*) وسرطان المعدة فقد أهملت عدة دراسات أخرى تربط بين البكتيريا والسرطان. وتمت في السنوات الماضية دراسة عدة أنواع من البكتيريا والفطريات وربطها مع الأورام السرطانية وأيضاً قدرتهم على حث الإلتهاب الذي قد يكون بدوره سبباً للأورام السرطانية. وكما يبدو أنه لا يوجد هناك نظرية واحدة للجرثومة المسرطنة وذلك للإعتقاد أن معظم أنواع البكتيريا قد تحدث تورماً سرطانياً. تم التركيز في هذا البحث مناقشة دور البكتيريا وأنواع من الأحياء الدقيقة الغير فيروسية في سرطان الفم. قد يبدو أن إهمال دور البكتيريا كمسبب للأورام السرطانية أدى إلى التقليل من فهمنا وإدراكنا لأهمية هذا الموضوع في الإصابة بالسرطان وبالتالي مما اعاق تطوير السبل العلاجية المناسبه له.

For over a century, non-virus microorganisms, notably bacteria have been implicated as causal agents of cancers, a relatively small number of researchers have provided evidence to support the so-called "cancer germ" hypothesis. With the exception of the link between *Helicobacter pylori* and stomach cancer, other supposed links have been ignored. A wide range of bacteria and other non-virus microbes, including fungi, have been implicated over the years in oncogenesis, as well as the ability to induce inflammation, which may cause cancer. It seems that there is no single "cancer germ," as most bacteria can apparently induce cancer. Here, the role of bacteria and other non-virus microorganisms and oral cancers will be discussed. By ignoring bacteria as a causal agent of cancer, we set back our understanding of this crucially important disease and, as a result, have hindered the development of potential cures.

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Although historical and more recent evidence shows that bacteria and other non-virus microbes play a role in oncogenesis, most of the cancer research community is unaware of, or else has dismissed, this potentially crucial association; this is certainly the case with oral cancer. The aim of this review is to highlight the role bacteria plays in cancer in general, and specifically in oral cancer. Oral cancer is the sixth most prevalent cancer worldwide and is particularly common in developing countries. For example, in Southeast Asia, approximately 40% of all malignancies are located within the oral cavity,[1] most of which are mainly squamous cell carcinomas (SCCs) that originate from the oral mucosa.[2] The mean all-stage survival rate for oral cancer over a 5 year period is <50%, with an annual mortality rate similar to that of malignant melanomas and cancers of the cervix.[3] The incidence of oral cancer is increasing worldwide, including in the United Kingdom[4] and in Saudi Arabia.[5] The male-to-female ratio has recently reduced significantly, whereas the number of cases in patients under 45 has increased remarkably.[3]

Bacteria and cancer. Historical reports of an etiological association between bacteria and cancer have been made from the mid-eighteen hundreds. In fact, almost as soon as the link was made between microorganisms, including fungi,[6,7] and bacteria, and disease,[8,9] Dudgeon & Dunkley reported that Doyen in 1886 has isolated a bacterium[10] for example, isolated a bacterium from 90% of the tumors he examined. This isolate was identified as *Micrococcus neoformans* and was subsequently shown to be a species of *Staphylococcus*.

Doyen[10] then went on to prepare a vaccine from the isolate and claimed it could cure cancer.[10] Additionally, Cantwell 1990 has reported that Glover in 1926 managed to isolate a specific bacterium from neoplastic tissue and created a serum which allegedly produced remarkable improvements in half of all treated cases.[11] Finally, a large number of non-virus microorganisms other than bacteria were also associated with human cancers, including species of protozoa and fungi (including yeasts), and members of every generation of microbiologists since the early days of interest in the supposed cancer germ hypothesis have reported a link between non-virus microbes and cancer.[7] Since this link was established over a century ago, the role of non-virus microbes in cancer has not been fully accepted. However, in addition to the scientific problems relating to its establishment, there are cultural reasons why the cancer germ hypothesis has not yet been accepted, and, as we shall see, even with increasing amounts of modern evidence based on the use of sophisticated, molecular identification techniques which support the link, the cancer community (including cancer charities) is either unaware of the association between non-virus microbes, notably bacteria, and cancer, or else chooses to ignore it.

In the twentieth century, Virgina Wuerthele as mentioned by Cantwell in 2005, isolated a bacterium, which she termed *Progenitor cryptoides*, that again claimed to generate a supposed cancer-curing vaccine.[12] Since such vaccines are obviously not in use today, they clearly must have been ineffective or, at best, variable. The main modern champions of the cancer germ hypothesis are Cantwell,[11,12] and Wainwright,[6,7,13-16] both of whom have provided evidence linking microbes with cancer and have attempted to convince the wider scientific and medical community of this possibility via various media outlets. Wainwright and Al Talhi,[16] published a study highlighting the isolation of a highly pleomorphic bacterium (*Bacillus licheniformis*) from a canine mammary tumor, which they suggested might be one of the cancer germs described in the early literature. A notable feature of this pleomorphic isolate is its ability to exist as bacterial rods and cocci as well as what appears to be frank fungus. Upon closer inspection; however, this "fungus" turns out to be a complex bacterial form that mimics a mass of hyphae and spores. It goes without saying that the ability of a tumor-isolated bacterium to present itself as a fungus, or as different bacterial forms, has caused considerable confusion among clinical bacteriologists, leading to claims that pleomorphic, cancer-isolated bacteria are contaminants or, at best, exist as mixed cultures. The ability of cancer-related bacteria to be pleomorphic is perhaps the single most important factor that has delayed the recognition of the ability of bacteria to play a role in carcinogenesis. This fact lead Wainwright[14] to title one of his papers on the subject, "*When heresies collide: Extreme bacterial pleomorphism and the cancer germ,*" with the heresies being: a) the existence of cancer-causing bacteria, and b) the ability of such bacteria to exist in widely different pleomorphic forms.

Another feature of the cancer germ hypothesis is the claim by cancer germ advocates that bacteria can live intracellularly, or even within the nucleus and are able to act as persisters, existing dormant for long periods within the host cell. Such claims may help explain why cancer is often associated with old age, namely, aging cells. Wainwright[17] also suggested that, due to their sub-micron size, nanobacteria can readily enter human cells and nuclei and may be particularly active in inducing cancers. While most people are happy to accept that viruses are involved in carcinogenesis due to their small size and seemingly "mysterious nature," bacteria tend to be considered prosaic organisms that seem to be incapable of inducing cancer. This presents us with yet another factor that helps to explain why the cancer germ hypothesis has long been neglected.

By far the most important discovery in relation to the cancer germ hypothesis came in the mid-1919's with the demonstration by Marshall 1995,[18] that the bacterium, *Helicobacter pylori (H. pylori)*, causes gastritis, which, in some cases, can lead to serious inflammation that causes gastric cancer.[19,20] Despite what is often thought, however, *H. pylori* is not the only bacterium (or non-virus microbe) that has recently been associated with cancer. Recent studies[21] reported that *Escherichia coli (E. coli)* and species of Salmonella systematically hone in on tumors where they replicate. Bacteria have also been associated with pancreatic cancers,[22] and some lung cancers are associated with *Chlamydia-based pneumonia* infections wherein inflammation is again the mechanism that leads to cancer development.[23] Notably, even as early as the 1920's, researchers linked the carcinogenic effect of microbes to this hypothesis.[15] Other recent links between bacteria and human cancers include the association between *Salmonella typhi* and both hepatobillary carcinoma,[24] and gall bladder cancer,[25] presumably due to its ability to convert bile salts to carcinogenic compounds.[26] Finally, an association

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between *Streptococcus bovis* and colorectal cancer (CRC) has also been shown,[27,28] which is possibly related to the production of pro-inflammatory chemokines.[29] As we have seen throughout more than 150 years of the cancer germ hypothesis, workers have claimed that cancer-causing bacteria are generally highly pleomorphic organisms. It is particularly noteworthy then that modern researchers have linked human cancers to a number of pleomorphic bacteria including, *H. pylori* and *Fusobacterium*, which are linked to CRC,[30] and *Chlamydia trachomatis*, which is associated with cervical cancer,[26] all of which are pleomorphic bacteria.

Oral bacteria and cancer. The association between microbes in the oral cavity and various types of cancers (**Table 1**) is becoming increasingly more recognized.[31,32] The microflora of the oral cavity includes a complex array of bacteria living in a balanced immune-inflammatory state with the host-patient, often existing in biofilms.[33] A variety of microorganisms have been associated with oral cancers, including *Exiguobacterium oxidotolerans, Prevotella melaninogenica, Staphylococcus aureus, Veillonella parvula*, and species of *Micrococcus*.[34] Other isolates found in oral cancers include yeasts, actinomycetes, Bifidobacteria, lactobacilli, and streptococci.[35] These are typically acidophilic organisms, which is not surprising since the micro-environment of solid tumors is generally hypoxic with a low pH, which favors the growth and survival of acid-tolerant bacteria.[36] *Streptococcus anginosus* has been particularly singled out as a potential causal agent of oral cancers largely due to its ability to induce inflammation.[37] *Streptococcus anginosus* is also associated with esophageal, gastric, and pharyngeal cancers.[38,39] Bacteria such as *Porphyromonas gingivalis (P. gingivalis)* are implicated in oral cancers[40] and interfere with this oral flora equilibrium, bringing the unbalanced host-bacteria relationships that allow organisms, such as *Fusobacterium nucleatum (F. nucleatum)*, to become dominant, opportunistic pathogens that cause periodontal disease. This series of events commonly occurs in patients with impaired immune systems and is becoming increasingly associated with the formation of oral cancers.[33] Viruses have also been widely implicated as a cause of oral cancers. Notably, Epstein barr virus (EBV) and human papilloma viruses (HPV)[41] as well as fungi, such as *Candida albicans*,[11] have all been associated with oral cancers. Chronic oral candidiasis often involves invasion of fungal hyphae into the oral epithelium, which leads to dysplastic changes and ultimately cancer.[42] Moreover, oral squamous cell carcinomas (OSCCs) also often contain higher numbers of *Porphyromonas* and *Fusobacterium* than do cells of nearby healthy mucosal membranes.[42] Several recent studies[43,44] have also shown a strong association between *F. nucleatum* and CRC, this bacterium is commonly found within, and close to CRC neoplasms, and it is frequently associated with lymph node metastases.

A variety of mechanisms have been suggested to explain how bacteria cause cancer. These include a) causing chronic infections, which lead to the production of toxins that then disturb the cell cycle and bring about altered cell growth,[45] b) infections can result in intracellular deposition of the pathogen, resulting in suppression of apoptosis via modulation of the expression of Bcl-2 family proteins, or inactivation of the retinoblastoma protein, pRb,[46] a set of

Table 1 - The association between microbes in the oral cavity and various types of cancers.

Study	Journal	Year	Title	Remarks
Nagy et al[42]	Oral Oncology	1998	The microflora associated with human oral carcinoma	Original article
Shiga et al[39]	Oncology Reports	2001	Presence of Streptococcus infection extra-oropharyngeal head and neck squamous cell carcinoma and its implication in carcinogenesis	Original article
Mager[8]	Journal of Translational Medicine	2006	Bacteria and cancer cause, coincidence or cure?	Review
Hooper et al[32]	Head Neck	2009	Exploring the link between microorganisms and oral cancer	Systematic Review
Chocolatewala et al,[35]	Indian Journal of Medical and Paediatric Oncology	2010	The role of bacteria in oral cancer	Review
Schwabe & Jobin[9]	Nature Reviews Cancer	2013	The microbiome and cancer	Review
Whitmore & Lamont[34]	PLOS Pathogens	2014	Oral bacteria and cancer	Review
Kerr[55]	The Journal of Dental Hygiene	2015	The oral microbiome and cancer	Update

circumstances that provides a niche that facilitates the survival of intracellular pathogens despite the immune system's attempts to destroy them by apoptosis, c) chronic infections induce cell proliferation and DNA replication by mitogen activated protein kinase (MAPK) pathways and cyclin D1, thereby increasing the incidence of cell transformation and the rate of tumor development, which result from enhanced genetic mutation,[47] d) pathogenic bacteria can cause chronic infections and subvert host cell signaling pathways, enhancing the survival of the pathogen,[26] e) bacteria can convert ethyl alcohol to acetaldehyde, which is carcinogenic by virtue of its ability to cause epithelial DNA damage, mutagenesis, and secondary hyper-proliferative epithelium,[48,49] and f) microbial carcinogenesis may also involve nitrosation by which microbes produce N-nitroso compounds from nitrites, amines, and amides. Filamentous fungi, many yeasts, and several bacterial species, including common species such as *E. coli*,[48] can catalyze nitrosation, and the production of carcinogenic nitrosamines appears to be particularly linked to cancer development in the oral cavity.[50] It is possible, however, that undetected cancers or precancerous lesions enhance the colonization and growth of oral bacteria and that these play no direct role in carcinogenesis.

Chronic inflammation has long been suggested as a factor that contributes tumor development.[51] For example, both *P. gingivalis* and *F. nucleatum* can cause chronic infections by persisting intracellularly within epithelial cells and initiating inflammatory responses. They can also spread systemically and cause infections beyond the oral cavity where they can cause major disruptions of the host's immune response mechanisms.[52] *Fusobacterium nucleatum* is markedly pro-inflammatory, and McCoy et al[43] pointed to a positive correlation between mRNA levels for several local cytokines and *Fusobacterium* species in CRC cases. *Fusobacterium nucleatum* produces a pro-inflammatory microenvironment, which enhances the development of CRC.[53] *Porphyromonas gingivalis* can also induce both pro- and anti-inflammatory effects, and in addition to general immune-disruptive effects, both *P. gingivalis* and *F. nucleatum* negatively impact a number of aspects of epithelial cell signaling, all of which are factors that are directly related to the development and progression of cancer.[54]

The oral cavity can be regarded a microbial niche that is home to numerous microbial communities made up of a variety of different organisms that exist in homeostasis with one another.[33] Certain bacteria within this community can affect the ability of the host to carry out immune surveillance, and, as a result, the oral microbiota enters a state of dysbiosis.[55] Under these new dysbiotic environmental pressures, previously commensal bacteria in the oral cavity, such as *F. nucleatum*, become opportunistic pathogens.[9] A positive correlation exists between the presence of *Fusobacterium species* and the mRNA levels of a variety of inflammatory cytokines, thereby demonstrating that these bacteria are potent inducers of inflammation.[43] These bacteria can also elevate levels of cell proliferation and migration by targeting signaling molecules, specifically kinases involved in cell cycle control.[34] Subsequent activation of the p38 protein by these kinases leads to the secretion of matrix metalloproteins 9 and 13, both of which play critical roles in the invasion and metastasis of tumors.[52] As a result, *F. nucleatum* acts as a potent pro-inflammatory agent and creates an environment in which the progression of cancer is highly favored.

Of course, it is also possible that bacteria enter tumors post tumorigenesis, as these organisms may have an affinity for the conditions that are created as the tumor develops.[8] Therefore, to confirm if a bacterial infection causes cancer, extensive research is required, specifically epidemiological studies linking the organism with cancer, molecular analysis of suspected pro-oncogenic virulence factors or toxins produced by the organism, and finally in vivo animal models where cancer can be monitored post-infection.

In conclusion, it is clear that the so-called cancer germ hypothesis has a very long history and that microbiologists and cancer researchers of every generation have reported such a link. Despite this however, bacteria are currently not widely accepted as a major cause of cancer. An exception to this notion is the role played by *H. pylori* in stomach cancers.[19] Strangely, the emphasis that has been placed on the ability of this bacterium to induce carcinogenesis has overshadowed the potential role of other bacteria in this process. It is as if *H. pylori* has been elevated to a "super-bacterium," which alone, amongst bacteria, can cause cancer. Simply put, if *H. pylori* can cause cancer, then there is no reason why other seemingly common place bacteria cannot do so also. The original supporters of the cancer germ hypothesis, including James Young, were clear in their minds that bacteria and other non-virus microbes cause cancer by initiating inflammation.[15] The cancer germ hypothesis states that a) bacteria and other non-virus microbes cause cancer in human and animals, b) there is no single "cancer germ," but that most, if not all, bacteria, even commonplace species such as *E. coli* and

S. aureus can induce cancer, and c) that bacteria exist both intracellularly and within the nucleus as persisters where they can evade the patient's immune system for very long periods of time, a fact which helps explain why cancer is a disease of old age. Essentially the theory claims that any microbe can cause cancer in humans if it is in the right place at the right time. If this is the case, then it suggests that it will be difficult to prevent or cure cancers if they have a microbial origin because no antibiotic can kill all bacteria. Additionally, it is impossible to sterilize the body completely, especially if the bacteria that induce cancer persist unseen by the immune system. Alternatively, it may be possible to develop vaccines against the main cancer-inducing bacteria. From the current standpoint, however, it seems that even if the cancer germ hypothesis is fully established, it will not necessarily lead to cure quickly. However, knowledge is power, and once the role that bacteria and other non-virus microbes play in human cancers, including oral cancer, is established, it will undoubtedly provoke increased efforts to produce a cure using many research avenues, including those that have not yet been defined.

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