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A Review of the Potential Role of Non-Virus Microbes in the Development of Oral and Other Cancers

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The view that bacteria, fungi and other non-virus microorganisms (NVMs) are involved in cancer has a long history and scientists of every generation have linked these common organisms with cancer, some even claiming that they developed vaccines which achieved cancer cures (Wainwright, 2010). The simple fact that the cancer germ hypothesis is not widely held today and that its application has not resulted in the demise of cancer suggests that either: 1) the idea is a non-starter, or 2) that cancer researchers continue to ignore the truth, namely that cancer in humans is largely a microbial disease. At first sight the first alternative would appear to be correct, but if this is the case why the link has persisted for more than a hundred years and why, even today, research papers are appearing which support a link between microorganisms and cancers? The aim of this review is to discuss the literature relating to the possibility that NVMs are involved in carcinogenesis, particularly in relation to oral cancers.

Key words: Non-Virus microbes, Oral and other cancers.

Oral Cancer

Oral cancer is one of the 10 most common cancers in the world with some 90% of the malignancies being squamous cell carcinomas (SCCs) which originate from the oral mucosa (Chen and Myers, 2001), oral cancer generally affects men in their sixties or seventies (Casiglia and Woo, 2001; Conway *et al*., 2006; Liewellyn *et al*., 2004), while the disease remains relatively rare in young adults (Annertz *et al*., 2002; Iype *et al*., 2004; Llewelyn *et al*., 2003; Oliver *et al*., 2000), it appears to be increasing in this cohort, as well as in women under 45 years (Hyde and Hopper, 1999; Worrall, 1995). A number of social habits and conditions have been linked to the increased risk of developing oral cancer, notably the use of tobacco and heavy alcohol consumption (Johnson, 2001), both of which appear to act synergistically (Pelucchi *et al*., 2008).

The large number of bacteria and other NVMs which live in the human oral cavity may play a role in cancer initiation and development? Over seven hundred taxa of bacteria have been isolated from the mouth, and yeast and filamentous fungi are also found here (Jenkinson and Lamont 2005; Mager *et al*., 2003), and as a result, the oral epithelium is continually exposed to a wide variety of microorganisms, some of which may initiate cancer.

Infection as risk factor in cancer in general

The association between cancer and NVMs has frequently been made, both in the

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historical and modern literatue (Wainwright, 2010). Patients with infectious endocarditis caused by *Streptococcus bovis* for example, apparently have an increased risk of developing colonic carcinoma (Ellmerich *et al*., 2000; Waisberg *et al*., 2002). Cervical infection with *Chlamydia trachomatis* has also been associated with an increased risk for the development of invasive cervical cancer. *Chlamydophil*a (previously known as *Chlamydia*) *pneumoniae* infections have also been linked to both malignant lymphoma and lung cancer in men (Kocazeyek, 2003). Infection with *Salmonella typhi* also increases the risk of gallbladder cancer in patients (Dutta *et al* 2000; Shukla *et al*., 2000). Recently, several species of bacteria have been found to both survive and grow within experimental solid tumors (Yu *et al.,* 2004) and appear to be shielded from the host immune system while hiding in these tissues (Lemmon *et al.,* 1997).

Infection with the yeast, *Candida* has been associated with malignant development in the oral cavity ever since it was found to cause candidal oral leukoplakias (Cawson 1969; Sitheeque and Samaranayake, 2003) and also to correlate with oral epithelial dysplasia (McCullough *et al.,* 2002). Candidal leukoplakia has been observed in rats when their tongues were artificially inoculated with *Candida* and long-term infection of the rat tongue caused both hyperplasia and dysplasia of the epithelium. The fact that epithelial dysplasia often improves after the elimination of *Candida* from infected tissue also points to a causal link (McCullough *et al.,* 2002). Chronic hyperplastic candidosis and associated hyphal invasion of the oral epithelium are also known to lead to the development of neoplasm in up to 10% of cases (Bartie *et al.,* 2004).

Bacteria associated with oral carcinoma

Several reports have suggested that patients with intraoral cancer possess an abnormal pathogen-rich bacterial population (Hooper *et al.,* 2006; Rice and Gill, 1976; Rice and Weimert, 1978). Bacteria which are involved in such abnormal mouth floras include both aerobes and anaerobes, including *Veillonella*, *Fusobacterium*, *Prevotella*, *Porphyromonas*, *Actinomyces*, *Clostridium*, *Haemophilus*, Enterobacteriaceae, and *Streptococcus* species. It is also suggested that dental plaque might provide a reservoir of the *Streptococcus. anginosus*, a bacterium which frequently infect oral and esophageal carcinomas (Sasaki *et al*., 2005). It has been suggested that patients with oral squamous cell carcinoma (OSCC) exhibit increased numbers of salivary bacteria compared to OSCC-free individuals, with numbers of bacteria such as *Capnocytophaga gingivalis*, *Prevotella melaninogenica*, and *S. mitis* being particularly increased in patients with this disease (Mager *et al.,* 2005); the possibility therefore exists of using these findings to develop a simple test for diagnosing oral cancer.

Possible mechanisms by which microbes may induce cancer

The development of OSCC involves a multistep process which requires genetic damage, often caused by exogenous carcinogens, and influenced by environmental factors and chronic inflammation. DNA damage can lead to mutation, which can result in the faulty aberrant expression of oncogenes and tumor-suppressor genes. Evidence suggests that numerous microorganisms bring about the initiation, promotion, or progression of cancer in humans. Some examples of how bacteria and *Candida* may be associated with carcinogenesis in humans, including nitrosamine compounds produced by *Candida* species, may indirectly or directly activate specific proto-oncogenes leading to the development of malignant lesions and N-nitroso-benzylmethylamine (NBMA) can induce carcinoma of the esophagus and the rat oral cavity (Fong *et al.,* 1986). Strains of *Candida* isolated from leukoplakia lesions also show a relatively high potential for producing NBMA from saliva (Krogh, 1990). An increasing number of studies provide evidence for the importance of an important role for Streptococci, and gram-positive aerobic bacteria, and yeasts in oral cancer via the production of acetaldehyde (Krogh, 1990; Kurkivuori *et al.,* 2006; Salaspuro, 2003; Vakevainen *et al.,* 2002).

Species of *Neisseria* species isolated from the oral cavity, for example, have been shown to exhibit very high levels of ADH activity and produce significant amounts of acetaldehyde in the presence of ethanol; increases in the microbial production of acetaldehyde correlates with smoking and heavy alcohol consumption. Such results point to the possibility that acetaldehyde is an important factor in the development of oral cancer.

Inflammation and carcinogenesis

Inflammation appears to increase the risk of cancer at many different body sites, including the pancreas, stomach, colon, liver, bladder, prostate, and ovaries (Chocolatewala *et al*., 2010). Epithelial inflammation is also a factor in oral carcinogenesis, and it is thought that inflammation is the mechanism that links the increase risk of this cancer with tobacco products and following the use of areca nut extract (Vishwanatha *et al*., 2003). Chronic inflammation promotes cancer development (Philip *et al.,* 2004) and such inflammation can be associated with microbial infection (Christen *et al.,* 1999; Macarthur *et al.,* 2004). For example, *H. pylori*, especially with strains positive for the cagA virulence factor, often result in an inflammatory response, which includes the induction of cyclooxygenase (COX)-2 expression and the invasion of the local tissue by neutrophils and phagocytes, accompanied by the production of pro-inflammatory cytokines (Sun *et al.,* 2004). *Helicobacter pylori* has also been shown to induce the activation of NADPH oxidase and produce oxygen radicals (Betten *et al*., 2001). Inflammation in the stomach is not however, caused solely by *H. pylori*; other species of bacteria can infect the stomach and hence may also play a role in gastric carcinogenesis; *Acinetobacter lwoffi*, for example, can also cause chronic gastritis independently of *H. pylori* (Cohen *et al.,* 2005). Several other associations between certain bacteria and cancers are based on inflammatory mechanisms. For instance, it has been suggested that *Propionibacterium acnes* infection may possibly be linked with the development of prostate cancer; this bacterium has been positively associated with a higher degree of prostatic inflammation, a condition which has in turn been implicated with carcinogenesis (Cohen *et al.,* 2005). *Propionibacterium acnes* is known to stimulate the production of inflammatory mediators (Graham *et al.,* 2004; Nagy *et al*., 2005). Similarly, the induction of inflammation may also explain the observed links between infections with *Chlamydophila pneumoniae* and *Streptococcus bovis* and an increased risk of lung and colon cancer, respectively; *C. pneumoniae* can also infect human lung epithelial cells and induce the expression of pro-inflammatory cytokines, including interleukin (IL)-8, interferon-c, and TNFa (Yang *et al.,* 2003). Likewise, *S. bovis* releases proteins which stimulate intestinal cells to produce inflammatory mediators such as IL-8 and prostaglandinE2 (PGE2), which also promotes the progression of pre-neoplastic lesions in the colonic mucosa of rats (Biarc *et al.,* 2004).

The vast numbers of bacteria residing within the human oral cavity do so without necessarily causing inflammation. However, as our knowledge of periodontal disease shows, given the correct circumstances some species of oral bacteria can initiate inflammation in their host (Delima *et al.,* 2002; Tlaskalova *et al.,* 2004). For example, *Porphyromonas gingivalis* can induce COX-2 expression (Kuramitsu *et al.,* 2002) and bring about an increased production of pro-inflammatory mediators such as TNF-a and cytokines including IL-6, IL-8, and IL-1b (Andrian *et al.,* 2004). Likewise, the periodontopathic species *Eikenella corrodens* is able to stimulate human oral epithelial cells to produce various mediators including IL-6 and IL-8, and PGE2, seemingly via the secretion of soluble proteins (Yumoto *et al.,* 2001). Oral species of *Streptococcus* isolated from carcinoma tissues have been found to be capable of promoting an inflammatory response. *Streptococcus anginosus* and *S. mitis* for example were found to induce the formation of inflammatory cytokines in human oesophageal epithelial cell lines and culture of *S. anginosus* contains an antigen which induces nitric oxide inflammatory cytokines synthesis in murine peritoneal exudates cells (Sasaki *et al.,* 2001) ; patients with periodontitis whose saliva tested positive for *S. anginosus* also show significantly higher levels of 8-hydroxy-deoxyguanosine (8-OHdG), a commonly used marker for evaluating inflammation and oxidative DNA damage. Increases in 8-OHdG levels have previously been associated with human premalignant lesions and cancerous tissues (Sugano *et al.,* 2003). Although the salivary levels of *S. anginosus* were relatively low in these patients, there was a correlation between the level of *S. anginosus* and 8-OHdG.128. It has also been hypothesized that *S. anginosus*, in particular, plays a significant role in many cases of esophageal cancer by causing inflammation and promoting the carcinogenic process. Eradication of these streptococci may lead to a decrease in the risk of recurrence of esophageal cancer (Sugano *et al.,* 2003).

Cellular proliferation has a pivotal role in carcinogenesis and mutations in DNA regularly arise from exposure to exogenous or endogenous mutagens (Butterworth and Goldsworthy, 1991). There have been several examples found of where bacteria suppress apoptosis and potentially promote carcinogenesis. For instance, *E. coli* releases a range of virulence factors including cytotoxic necrotizing factor type 1 (CNF1), which prevents apoptosis in epithelial cells, ostensibly by activating a cell signalling cascade and promoting the expression of antiapoptotic members of the Bcl-2 gene family (Fiorenitini *et al.,* 1998); *C. pneumoniae*-infected epithelial cells are also resistant to apoptosis induced by chemicals or death receptors (Gerlic *et al*., 2004). Species of *Mycoplasma* such as *M. fermentans* and *M. penetrans* also prevent apoptosis *in vitro* and *M. fermentans* has also been shown to inhibit apoptosis in a human cell line (Gerlic *et al.,* 2004). A number of mycoplasmal species, including *M. fermentans*, are components of the normal oral microflora in saliva, on the mucosal surfaces, and in plaque (Chingbingyong and Hughes 1996; Paster *et al.*, 2001; Shibata *et al.,* 1999). There is as yet, however, no evidence to link *Mycoplasma*-related suppression of apoptosis with carcinogenesis of the oral cavity.

CONCLUSION

The possibility that bacteria and other non-virus microorganisms (NVMs) can cause cancer has been discussed at length for more than a century and each generation of microbiologist has isolated so-called "cancer germs" and suggested that they play a direct role in the aetiology of cancer in humans (Wainwright, 1998). The link between cancer and NVMs continues to be demonstrated with the aid of modern research technologies, including molecular microbiology (Wainwright, 2006; Wainwright; 2002; Stein and Katz, 2010; Lax 2002; Hooper *et al*., 2006); modern research has also been directed to the role of bacteria in oral cancers (Hooper *et al.,* 2006). Nevertheless, the role of bacteria and fungi in cancer aetiology remains generally overlooked; the obvious exception being the suggested role for *H. pylori* in gastric cancer. This neglect, it could be argued, is due to a lack of sufficient convincing evidence which demonstrates such a link. Alternatively cultural factors may be working against the view that this link exists. One might have imagined that the recognition that *Helicobacter* species are involved in carcinogenesis would have led to huge investment in research aimed at determining the role of other bacteria, and NVMs in general, in the aetiology of cancer. Surprisingly, this has yet to happen, and the fact that *Helicobacter* species cause cancer has not resulted in the cancer–research establishment accepting the possibility that other, and perhaps most, bacteria can also do so. Since there is nothing particularly special about *H. pylori* (other than it possesses a number of unique features relevant to its existence in the acidic environment of the stomach) there is no obvious reason why its ability to induce cancer should not be shared by other bacteria and NVMs.

A "cancer germ hypothesis" based on what we currently know about the relationship between NVMs and bacteria would include the following points:

1) It seems that most microorganisms, including bacteria, fungi, protozoa and viruses can, under the appropriate circumstances, cause cancer. It appears however, unlikely that a single cancer germ, or single cancer-causing group is involved although some organisms are probably better adapted to the role of cancer-causing agents.
2) It appears that some NVM can lie dormant for long periods within the cell or nucleus from where they induce oncogenesis. This intracellular existence may be favoured by the ability of bacteria to exist as ultra-small, or cell- wall deficient forms.
3) Non virus microorganisms appear to be able to promote carcinogenesis using a wide range of mechanisms, notably by the involvement of inflammation and toxins.
4) The complexity of the interaction between cancer and NVMs suggest that it will probably be difficult to prove that such organisms cause carcinogenesis. Similarly, the fact that a diverse range of common microbes potentially causes carcinogenesis means that it will be difficult to treat cancers by removing a single organism or taxonomic

group. It may however, be possible to inhibit some carcinogenic function that is common to most NVMs, including their ability to act as intracellular peristors, or produce cell wall or pleomorphic forms, toxins or inflammation-inducers. In short, it may prove more fruitful to attack specific cancer-inducing processes shared by many NVMs, rather than trying and eliminate individual, so-called, cancer germs. Similarly, there is an indication from the cancer-literature that the potential role of NVMs in cancer is being taken more seriously, a fact which is borne out by the recent appearance, of major reviews on the subject (Vogelmann and Amieva, 2007; Kuper *et al.,* 2000). In the absence of a massive research effort directed towards determining the role of non-virus microbes in carcinogenesis, it is likely however, that we will face another century or so when the solution to the enigma of cancer may be obvious, only to remain overlooked.

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