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Periodontal microorganisms and diagnosis of malignancy: A cross-sectional study

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Abstract.
BACKGROUND: Oral infections associate statistically with cancer.
OBJECTIVE: We hypothesized that certain periodontal microorganisms might specifically link to malignancies in general and set out to investigate this in our ongoing cohort study.
METHODS: A sample of 99 clinically examined patients from our cohort of 1676 subjects was used to statistically investigate the associations between harboring periodontal microorganisms *Aggregatibacter actinomycetemcomitans* (*A.a*), *Porphyromonas gingivalis* (*P.g*), *Prevotella intermedia* (*P.i*), *Tannerella forsythia* (*T.f*) and *Treponema denticola* (*T.d*). We used oral infection indexes and the incidence figures of malignancies as registered in 2008–2016 in the Swedish National Cancer Register.
RESULTS: The pathogen *A.a* showed strong association with malignancy in 32 out of the 99 patients while *P.g* and *P.i* were more prevalent among patients without malignancy. In principal component analyses, *A.a* appeared in the strongest component while the second strongest component consisted of a combination of *T.f* and *T.d*. The third component consisted of a combination of *P.g* and *P.i,* respectively. Of basic and oral health variables, gingival index appeared to be the strongest expression of inflammation (Eigen value 4.11 and Explained Variance 68.44 percent).
CONCLUSIONS: The results partly confirmed our hypothesis by showing that harboring certain periodontal bacteria might link to malignancy. However, the associations are statistical and no conclusions can be drawn about causality.

Keywords: Bacteria, cancer, epidemiology, malignant disease, periodontitis

1. Introduction

Cancer is the number two killer in industrialized countries – after cardiovascular diseases, heart infarction and stroke. Inflammation has been estimated to play a role in 15 –20% of all malignancies. The cellular pathways include genetic events leading to malignant transformation and tumor-infiltrating leukocytes are the principal regulators of cancer associated inflammation [1].

The highly prevalent oral infections represent a huge inflammatory burden, both at the individual and population level, associating with a number of systemic diseases. Cardiovascular diseases, malignancies, diabetes, and even death, are indeed statistically linked to oral infections, particularly associating with periodontal disease [2–5].

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We have earlier shown, in our ongoing register study the association of periodontal diseases to different kinds of cancer [4, 6, 7]. Further, in the same cohort, even history of oral infections was reported to be associated with cancer [8]. Certain genetic profiles may explain part of these associations by rendering a subject liable to the development by guiding the inflammatory processes [9]. But it seems that the key role here is played by the oral microbiota [10]. Infections caused epithelial ulcerations in the mouth provide a potential path of entry to the circulation for numerous oral microorganisms. These have been detected in atheromatous plaques, for example, and pro-inflammatory mediators, such as C-reactive protein and a number of cytokines, are also elevated in the presence of oral infections [11, 12]. Signaling molecules, such as tumor necrosis factor, interleukin 1 and interleukin 6 can enter the circulation via the periodontal microcirculation and affect at distant sites [13]. Chronic inflammation, like in periodontal diseases, may then cause malignant transformation in a number of organs with consequent tumor development [14].

A recent meta-analysis by Xiao et al. [15] showed that infection with periodontal bacteria increased the incidence of cancer with odds ratio (OR) 1.25 (95% confidence interval (CI) 1.03–1.52) and that it also linked to mortality. This risk was particularly associated with *Porphyromonas gingivalis* (*P.g)* infection (OR = 2.1; CI 1.34–3.47) and *Prevotella intermedia (P.i*) infection (OR = 1.28; CI 1.01–1.63). Subsequently, with this background we set out to investigate in our longitudinal databases the associations between specific oral bacteria and the prevalence of malignant diseases. Our hypothesis was that harboring certain periodontal microorganisms increases the risk of malignancy.

2. Subjects and methods

2.1. The cohort

The subjects of this study derive from our 30-year Swedish cohort study explained in detail in earlier publications [3, 16, 17]. In brief, the original cohort was selected in 1985 using the registry file of all inhabitants of the Stockholm metropolitan area, and consisted of 3273 individuals (born on the 20th of any month between the years 1945 to 1954) of whom 1676 were clinically examined. The focus was on the prevalence of periodontal disease of the subjects. Periodontal health indexes, namely, Plaque Index (PI), Calculus, Gingival Index (GI), Periodontal Probing Depth (PD), Bleeding on Probing (BOP), and Periodontal Attachment Loss (AL) had been calculated. Follow-up investigations were conducted in 2003 and 2009, respectively, and the present microbiological data is from the last examination where 99 subjects participated. They had been originally selected by a computer program to match the gender and age of the subjects with respect to their original periodontal status (yes/no periodontitis). Details of this subset material has been described earlier by Yakob and coworkers [18]. The individuals of the cohort are registered in the nationwide Hospital Admission Database and Death Register of the Center of Epidemiology, Swedish National Board of Health and Welfare. Diseases were classified according to the WHO International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10). The socio-economic data such as age, education, yearly income, social status, and working status, are obtained from the National Statistics Centre, Örebro, Sweden. The study has been approved by Ethics Committee of the Karolinska University Hospital at Huddinge (Dnr 2007/1669–31; 2012/590–32; 2017/2204–32). All subjects gave their informed consent to participate.

2.2. Recording the malignancies

The diagnoses of malignancies were extracted from the Swedish Cancer Register included in the above-mentioned national health registers. For the present study, the cumulative diagnoses of malignancies in the years 2008 – 2016 were extracted from the Register.

Table 1
Basic characteristics of the participants with and without malignancy, presented as number and (percentage)

	With malignant diagnoses	Without malignant diagnoses
Number	32	67
Men	17 (44%)	38 (57%)
Women	15 (56%)	28 (42%)
Age*	59.3 ± 3.0	58.2 ± 2.9
Smoker	14 (44%)	33 (49%)
Non-smoker	18 (56%)	33 (49%)

*Mean with standard deviation.

2.3. Analyses of periodontal microorganisms

According to the method of Jin et al. [19], gingival crevicular samples from four periodontal test sites were collected from the subjects. The samples were immediately centrifuged (8000 g) for 5 min at 4°C, and the supernatants and pellets were frozen to –70°C until analyzed. The pellets were then prepared for polymerase chain reaction (PCR), and the periodontitis associated bacteria *Aggregatibacter actinomycetemcomitans* (*A.a*), *Porphyromonas gingivalis* (*P.g*), *Prevotella intermedia* (*P.i*), *Treponema denticola* (*T.d*) and *Tannerella forsythia* (*T.f*) were detected non-quantitatively, present or not present. Specific primers were designed to hybridize to various regions of 16S rRNA genes [20, 21]. Results are expressed in percent (%) if at least one site of the periodontal pockets was detected positive.

2.4. Statistical analysis

Descriptive statistics and associations between cancer, latent components of bacteria and of clinical variables were computed. The associations were estimated with logistic regression analysis and latent components of bacteria types and of clinical variables were estimated by principal component analysis. The analyses were conducted in SPSS 25.0 software environment.

3. Results

Characteristics of the subjects are shown in Table 1. The frequency of women and number of non-smokers was somewhat higher among patients with malignancy but there were no statistically significant differences between the two groups with and without malignancy in this regard.

Diagnoses of the malignancies of the 32 patients as well as the periodontal clinical variables are demonstrated in Table 2 and Table 3, respectively. The microbial findings are presented in Table 4. Among the analyzed periodontal bacteria, *A.a* was more prevalent among cases with malignancy compared with cases without, while *P.i* and *P.g* showed higher prevalence among the subjects without malignancy. As can be seen in Table 4, the 95% intervals for the estimated proportion of cases in the group with malignancies compared with the group without malignancies does not overlap for *P.g* but does overlap for *A.a*, *P.i* and *T.f*, and markedly for *T.d*. This result indicates a difference between the groups regarding *P.g* as it is included in the component 3 (Table 7).

Results of the principal component analyses are presented in Tables 5 and 6. The five types of bacteria loaded in the three latent components showed that *A.a* loaded in the strongest component, (loading 0.971, component 1, Eigen value 1.71), while the second strongest component (component 2,

Table 2
Diagnoses of the malignancies of the 32 patients

Diagnosis	Women (n)	Men (n)
Breast cancer	3	2
Prostate cancer		3
Epidermoid cancer		1
Skin cancer		1
Oseophagus cancer	1	
Lymphatic leukemia	1	1
Pancreas cancer		1
Non-Hodgkin lymphoma	1	1
Liver cancer	1	1
Bladder cancer		1
Uterus cancer	3	
Colon cancer	1	1
Lung cancer		1
Brain tumor	1	1
Sarcoma	1	
Lip cancer		2
Rectum cancer	1	
Gut cancer	1	

Table 3
Median and interquartile range (IR) for the included clinical variables

Clinical variable	Median (and IR) of all participants	Median (and IR) of patients with no malignancy	Median (and IR) of patients with malignancy
Plaque index	0.6 (0.5)	0.6 (0.5)	0.5 (0.6)
Calculus	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)
Gingival index	0.7 (0.7)	0.7 (0.6)	0.8 (0.9)
Pocket depth	2.7 (0.6)	2.7 (0.6)	2.6 (0.8)
Bleeding on probing	0.4 (0.4)	0.4 (0.4)	0.4 (0.5)
Attachment loss	3.2 (0.8)	3.2 (0.6)	3.2 (0.8)

Table 4
Proportion of cases (percentage and 95% confidence interval) of the investigated microorganisms

Type of bacteria	Cases without malignancy	Cases with malignancy
A.a	14.9 (6.4–23.4)	25.0 (10.0–40.0)
P.i	68.7 (57.6–79.8)	56.3 (39.2–73.4)
P.g	56.7 (45.5–67.9)	28.1 (12.5–43.6)
T.d	56.7 (45.5–67.9)	65.6 (49.2–82.0)
T.f	86.6 (78.5–94.2)	75.0 (49.8–90.2)

A.a = *Aggregatibacter actinomycetemcomitans*; *P.i* = *Prevotella intermedia*; *P.g* = *Porphyromonas gingivalis*; *T.d* = *Treponema denticola*; *T.f* = *Tannerella forsythia*.

Table 5
Principal component analysis of the investigated periodontal microorganisms

Component no.	Eigen value	Explained variance	Cumulative frequency
1	1.71	34.13	34.13
2	1.11	22.19	56.32
3	1.00	20.09	76.41

Table 6
Factor loadings for each clinical variable in clinical inflammation

Clinical variable	Factor loadings
PI	0.861
Calculus	0.711
GI	0.921
PD	0.831
BOP	0.883
AL	0.736

PI = Plaque index, GI = gingival index, PD = periodontal pocket depth, BOP = bleeding on probing index, AL = alveolar bone attachment loss.

Table 7
Logistic regression of malignancy status by using the four components (clinical variables, Component 1 *A.a,* Component 3 *P.g* and *P.i,* and Component 2 *T.d* and *T.f*) as explanatory variables

Components	Beta	Standard error	Wald chi-square	Df	p	OR	95% CI	
							Low	High
Clinical inflammation	0.034	0.270	0.016	1	0.900	1.034	0.610	1.756
Component 1 *A.a*	0.422	0.236	3.20	1	0.074	1.526	0.960	2.423
Component 3 *P.g* and *P.i*	–0.757	0.267	8.035	1	0.005	0.469	0.278	0.792
Component 2 *T.d* and *T.f*	–0.175	0.257	0.465	1	0.495	0.839	0.507	1.389
Age	0.137	0.102	1.783	1	0.182	1.147	0.938	1.401
Gender	0.439	0.508	0.745	1	0.388	1.551	0.573	4.198
Smoking	–0.018	0.482	0.001	1	0.974	0.984	0.383	2.530

A.a: *Aggregatibacter actinomycetemcomitans*; *P.i*: *Prevotella intermedia; P.g*: *Porphyromonas gingivalis*; *T.d*: *Treponema denticola*; *T.f*: *Tannerella forsythia*; CI: confidence interval. Adjusted for age, gender and smoking.

Eigen value 1.11) consisted of a combination of bacteria *T.f* (loading 0.704) and *T.d* (loading 0.869), respectively. The third component consisted of the combination of *P.g* (loading 0.754) and *P.i* (loading 0.846), respectively. Results from the principal component analysis of all the six clinical oral health variables, namely, PI, Calculus Index, GI, PD, BOP, and AL, are given in Table 6. When loaded in one and the same latent component, clinical inflammation, with Eigen value 4.11 and Explained variance 68.44 percent, GI appeared to be the strongest marker of inflammation (Table 6).

Results from the logistic regression analysis are given in Table 7. After controlling for the confounder variables age, gender and smoking, the component consisting of bacteria *P.g* and *P.i* was significantly protective against malignancy, while the component 1 consisting of bacteria *A.a* showed a strong

tendency to be positively associated with malignancy. The distribution of smokers versus non-smokers among those with and without malignancy was not significantly different according to a Chi-2 test (Chi-2 = 0.337, df = 1, $p = 0.561$). The correlation between malignancy and smoking was shown to be extremely low and negative (–0.059) in this material.

4. Discussion

In the present study with health register background extending for 30 years, we demonstrate how the prevalence of certain periodontal bacteria linked to the incidence of malignancy. Specifically, *A.a* a known virulent periodontal microorganism showed a strong association. Previously, this bacterium has been associated in particular with atherosclerosis and serum lipid aberrations [22]. The pathogenic mechanisms of *A.a* are based on its leukotoxicity but it also has other cytotoxic and genotoxic characteristics [23]. Thus, the theoretical basis is solid why *A.a* in the present investigation showed a strong association with malignancy.

P.g, another much studied oral pathogen was shown to be associated with *P.i*. In fact, in the present study, *P.g* combined with *P.i* appeared protective against malignancy, which indeed was contrary to what we had expected. Namely, *P.g* has been earlier associated with a number of malignancies, including gastro-intestinal cancers [24]. Xiao and co-workers in their aforementioned meta-analysis observed a strong association between *P.g* and cancer (OR 1.86; CI 1.20 – 2.88) while *T.f* showed a weak association with cancer (OR 1.06; CI 0.80 – 1.41) [15]. Notably, *T.f* has earlier been associated with esophageal cancer [25].

Furthermore, Fitzsimonds et al. [26]. recently reported that *T.d* is among the species that are enriched in oral cancer. This spirochete is an oral pathogen associated with periodontal disease but it is not as extensively studied as the other bacteria here analyzed. In the present study, *T.d* loaded together with *T.f* in a component that was not significantly associated with malignancy. The finding certainly calls for more studies.

The bacterium *P.i* is considered to be less virulent compared with the other oral bacteria here analyzed, and it indeed appeared to be protective. However, *P.i* has also been reported to link to colorectal cancer, particularly in the proximal colon cancer [27]. But it must be emphasized that detection of a bacterium at a specific site with malignancy does not tell anything about the etiology. Oral bacteria like *P.i* might as well be there as innocent bystanders because of the frequent access of oral microorganism into blood circulation. In an animal model, *P.i* has nevertheless been shown pathogenic characteristics in inducing pneumonia [28]. The bacterium has also been reported to induce cytokine response in oral biofilm [29].

When it comes to the clinical variables, it was shown that all six variables registered loaded in one latent component, namely clinical inflammation. The strongest marker of inflammation was shown to be GI. This means that it might be sufficient to assess GI when estimating oral inflammation in future studies.

In general, however, when discussing the eventual role of individual bacteria in the development of - or association with - malignancy the results must be interpreted with caution. It is clear that the scientific evidence is very weak and based on few studies only with limited numbers of case-specific malignancies [30]. Hence, our present results must also be taken as suggestive rather than conclusive, but they may be used for novel hypothesis generation. In the future, much larger subject materials are needed than here analyzed. Due to practical reasons we had the microbiological data derived only from the 2009 clinical examination of the subjects. It might also be important in further studies to investigate the role of the whole oral microbiome and possible changes in its composition during the course and treatment of malignant diseases. The first steps have already been taken in this regard but so far, the

results are controversial [31, 32]. It should also be kept in mind in this discussion that microorganism may indeed also have a protective role in carcinogenesis [33, 34].

In the present study, most of the recorded malignancies were cancers where the role of inflammation is well established [35]. On the other hand, inflammation has been reported to play a role also in the development of other malignancies like leukemia, sarcoma and brain tumors, also here encountered. Thus, pooling all the malignancies together for current analyses was entitled [36, 37]. The strength of our present study is the long observation time as regards the development of malignancies in the cohort. The main weakness, however, is the small number of patients available for the cross-sectional analyses. This fact may also explain the unexpected observation that smoking in our patients did not link to cancer. Nevertheless, our study hypothesis was partly confirmed by showing interesting associations between the prevalence of oral bacteria and the cumulative occurrence of malignancies, but further studies are indeed needed for final conclusion. Finally, we need to re-emphasize that the current results do not entitle any assessment of causality.

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Author contributions

All authors contributed equally.

Conflict of interest

The authors declare no potential conflicts of interests.

References

[1] Chang AH, Parsonnet J. Role of bacteria in oncogenesis. Clin Microbiol Rev. 2010;23(4):837-57.
[2] Meurman JH, Sanz M, Janket SJ. Oral health, atherosclerosis, and cardiovascular disease. Crit Rev Oral Biol Med. 2004;15(6):403-413.
[3] Soder B, Jin LJ, Klinge B, Soder PO. Periodontitis and premature death: a 16-year longitudinal study in a Swedish urban population. J Periodontal Res. 2007;42(4):361-66.
[4] Soder B, Andersson LC, Meurman JH, Soder PO. Unique database study linking gingival inflammation and smoking in carcinogenesis. Philos Trans R Soc Lond B Biol Sci. 2015;370(1661):20140041.
[5] Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356(9):911-20.
[6] Soder B, Yakob M, Meurman JH, Andersson LC, Klinge B, Soder PO. Periodontal disease may associate with breast cancer. Breast Cancer Res Treat. 2011;127(2):497-502.
[7] Soder B, Yakob M, Meurman JH, Andersson LC, Soder PO. The association of dental plaque with cancer mortality in Sweden. A longitudinal study. BMJ Open. 2012;2(3).

[8] Virtanen E, Soder B, Andersson LC, Meurman JH, Soder PO. History of dental infections associates with cancer in periodontally healthy subjects: a 24-year follow-up study from sweden. J Cancer. 2014;5(2):79-85.
[9] Janket SJ, Javaheri H, Ackerson LK, Ayilavarapu S, Meurman JH. Oral Infections, Metabolic Inflammation, Genetics, and Cardiometabolic Diseases. J Dent Res. 2015;94(9 Suppl):119S-127S.
[10] Meurman JH. Oral microbiota and cancer. J Oral Microbiol. 2010;2.
[11] E. Virtanen. *Degree Thesis*. Chronic dental diseases and systemic health: cardiovascular diseases and cancer. University of Helsinki and Helsinki University Hospital, Helsinki 2018, ISBN 978-971-51-4496-9.
[12] Pejcic A, Kesic L, Milasin J. Association between periodontopathogens and CRP levels in patients with periodontitis in Serbia. J Dent Res Dent Clin Dent Prospects. 2011;5:10-6.
[13] Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc. 2008;139(Suppl):19S-24S.
[14] Nwizu N, Wactawski-Wende J, Genco RJ. Periodontal disease and cancer: Epidemiologic studies and possible mechanisms. Periodontol 2000. 2020;83(1):213-33.
[15] Xiao L, Zhang Q, Peng Y, Wang D, Liu Y. The effect of periodontal bacteria infection on incidence and prognosis of cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2020;99(15):e19698.
[16] Soder PO, Jin LJ, Soder B, Wikner S. Periodontal status in an urban adult population in Sweden. Community Dent Oral Epidemiol. 1994;22(2):106-11.
[17] Soder PO, Soder B, Nowak J, Jogestrand T. Early carotid atherosclerosis in subjects with periodontal diseases. Stroke. 2005;36(6):1195-200.
[18] Yakob M, Kari K, Tervahartiala T, Sorsa T, Söder PÖ, Meurman JH, Söder B. Associations of periodontal microorganisms with salivary proteins and MMP-8 in gingival crevicular fluid. J Clin Periodontol. 2012;39:256-63.
[19] Jin LJ, Soder PO, Leung WK, Corbet EF, Samaranayake LP, Soder B, Davies WI. Granulocyte elastase activity and PGE2 levels in gingival crevicular fluid in relation to the presence of subgingival periodontopathogens in subjects with untreated adult periodontitis. J Clin Periodontol. 1999;26(8):531-40.
[20] Wahlfors J, Meurman JH, Vaisanen P, Alakuijala P, Korhonen A, Torkko H, Janne J. Simultaneous detection of Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis by a rapid PCR method. J Dent Res. 1995;74(11):1796-801.
[21] Meurman JH, Wahlfors J, Korhonen A, Alakuijala P, Vaisanen P, Torkko H, Janne J. Identification of Bacteroides forsythus in subgingival dental plaque with the aid of a rapid PCR method. J Dent Res. 1997;76(7):1376-80.
[22] Pietiainen M, Kopra KAE, Vuorenkoski J, Salminen A, Paju S, Mantyla P, Buhlin K, Liljestrand JM, Nieminen MS, Sinisalo J, et al. Aggregatibacter actinomycetemcomitans serotypes associate with periodontal and coronary artery disease status. J Clin Periodontol. 2018;45(4):413-21.
[23] Belibasakis GN, Maula T, Bao K, Lindholm M, Bostanci N, Oscarsson J, Ihalin R, Johansson A. Virulence and Pathogenicity Properties of Aggregatibacter actinomycetemcomitans. Pathogens. 2019;8(4).
[24] Olsen I, Yilmaz O. Possible role of Porphyromonas gingivalis in orodigestive cancers. J Oral Microbiol. 2019;11(1):1563410.
[25] Malinowski B, Wesierska A, Zalewska K, Sokolowska MM, Bursiewicz W, Socha M, Ozorowski M, Pawlak-Osinska K, Wicinski M. The role of Tannerella forsythia and Porphyromonas gingivalis in pathogenesis of esophageal cancer. Infect Agent Cancer. 2019;14:3.
[26] Fitzsimonds ZR, Rodriguez-Hernandez CJ, Bagaitkar J, Lamont RJ. From Beyond the Pale to the Pale Riders: The Emerging Association of Bacteria with Oral Cancer. J Dent Res. 2020;99(6):604-12.
[27] Dai Z, Coker OO, Nakatsu G, Wu WKK, Zhao L, Chen Z, Chan FKL, Kristiansen K, Sung JJY, Wong SH, et al. Multicohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. Microbiome. 2018;6(1):70.
[28] Nagaoka K, Yanagihara K, Morinaga Y, Nakamura S, Harada T, Hasegawa H, Izumikawa K, Ishimatsu Y, Kakeya H, Nishimura M, et al. Prevotella intermedia induces severe bacteremic pneumococcal pneumonia in mice with upregulated platelet-activating factor receptor expression. Infect Immun. 2014;82(2):587-93.
[29] Fteita D, Kononen E, Gursoy M, Ma X, Sintim HO, Gursoy UK. Quorum sensing molecules regulate epithelial cytokine response and biofilm-related virulence of three Prevotella species. Anaerobe. 2018;54:128-35.
[30] Mai X, Genco RJ, LaMonte MJ, Hovey KM, Freudenheim JL, Andrews CA, Wactawski-Wende J. Periodontal Pathogens and Risk of Incident Cancer in Postmenopausal Females: The Buffalo OsteoPerio Study. J Periodontol. 2016;87(3):257-67.
[31] Healy CM, Moran GP. The microbiome and oral cancer: More questions than answers. Oral Oncol. 2019;89:30-33.
[32] Chattopadhyay I, Verma M, Panda M. Role of Oral Microbiome Signatures in Diagnosis and Prognosis of Oral Cancer. Technol Cancer Res Treat. 2019;18:1533033819867354.

[33] Shuwen H, Miao D, Quan Q, Wei W, Zhongshan Z, Chun Z, Xi Y. Protective effect of the "food-microorganism-SCFAs" axis on colorectal cancer: from basic research to practical application. J Cancer Res Clin Oncol. 2019;145(9):2169-97.
[34] Sivamaruthi BS, Kesika P, Chaiyasut C. The Role of Probiotics in Colorectal Cancer Management. Evid Based Complement Alternat Med. 2020;2020:3535982.
[35] Parsonnet J. Bacterial infection as a cause of cancer. Environ Health Perspect. 1995;103(Suppl 8):263-68.
[36] Giles FJ, Krawczyk J, O'Dwyer M, Swords R, Freeman C. The role of inflammation in leukaemia. Adv Exp Med Biol. 2014;816:335-360.
[37] Radons J. The role of inflammation in sarcoma. Adv Exp Med Biol. 2014;816:259-313.