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Investigation of the Association between Periodontal Disease Indices and Risk of Acute Hematopoietic Cancer Development (Acute Myeloid and Acute Lymphoblastic Leukemia): A Case – Control Study

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Abstract

The objective of the current research was to investigate the possible association between Periodontal Disease indices and risk of development Acute Hematopoietic Cancer (Acute Myeloid and Acute Lymphoblastic Leukemia) in a representative Greek adult sample. 174 individuals with Acute Myeloid and Acute Lymphoblastic Leukemia-cases and 174 matched healthy individuals- controls underwent an oral and dental clinical examination and completed a questionnaire. The periodontal condition for cases and controls included Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL) and Gingival Index (GI). Chi-square test and logistic regression models were carried out to assess the possible association. The logistic regression model showed that CAL (p= 0.054) (OR= 2.467, 95% CI= 1.177-2.231), and GI (p= 0.043) (OR = 3.352, 95% CI= 1.285-4.745), were marginally significantly associated with an increased risk of developing Acute Hematopoietic Cancer.

Keywords: Periodontal disease; Acute myeloid leukemia; Acute lymphoblastic leukemia; Risk factors; Adults.

1. Introduction

Hematopoietic cancer includes Acute Lymphoblastic Leukemia(ALL), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia(CLL),Chronic Myeloid Leukemia(CML), and Multiple Myeloma (MM) [1]. AML is the most common hematopoietic cancer among adults and is responsible for 80% of all cases. The main feature of the disease is the immature blast cells clonal expansion in the bone marrow and peripheral blood, leads to insufficient erythropoiesis and bone marrow failure [2-4]. Approximately the new cases among males and females are about 4.2 per 100,000 individuals, whereas in the U.S the annual incidence has been estimated to be more than 20,000 cases. The disease is more prevalent among males compared with females, with a ratio 5:3, whereas at the time of clinical diagnosis the average age is about 65 years [5]. In 2018, the number of leukemic patients around the world reached 437, 033 cases and it is expected to rise to 23.6 million case per year by 2030 [6]. The most common risk factor for AML are hematological disorders such as myelodysplastic syndrome, myelofibrosis, polycythemia vera or thrombocythemia, and aplastic anemia. Other risk factors that also increase AML risk are congenital diseases such as Down and Bloom syn-drome, whereas environmental exposures like radiation, tobacco smoking,

chemical exposure, (benzene) and previous exposure to cancer treatment (chemotherapy/ radiotherapy) agents have also been suggested [7-14].

The 3-year survival rate is 9-10% and the 5-year survival is 3-8% in individuals aged 60 years and older, compared with 5-year survival rates of up to 50% for younger patients [15-17]. ALL is a B- or T-lymphoblasts malignancy, histologically characterized by abnormal unlimited proliferation, immature lymphocytes and their progenitors which ultimately results in the substitution of bone marrow cells and other lymphoid organs leading to a classis disease standard characteristic of ALL [18]. ALL represents 2 % of the lymphoid neoplasms diagnosed in the U.S, whereas appears to a slight extend to be more common in males than females [18-20]. ALL affects about 4,000 indivi-duals in the U.S each year with the majority being under the age of 18, whereas the peak age of diagnosis is between two and ten years of age. The disease has low incidence overall in population as is about 3.3 cases per 100,000 children. ALL etiology is unknown [21], however is more frequent in children with Down , Bloom, and Li- Fraumeni syndromes, neurofibromatosis type I, and ataxia telangiectasia [22]. Certain environmental factors have been involved in ALL etiology such as exposure to chemical agents (benzene), ionizing radiation, and previous exposure to chemotherapy or radiotherapy, whereas ALL is not regarded a familial disease [22]. The role of electromagnetic fields or pesticides in ALL etiology remains unclear [23, 24], whereas it been hypothesized that an abnormal immune response to a common infection may be involved in ALL etiology [24]. Survival rates for ALL have improved dramatically and a current 5-year overall survival rate estimated at greater than 85 % [25]. Periodontal disease (PD), gingivitis and periodontitis is a chronic microbial inflammatory disease of the periodontal tissue, and with dental caries are the main reasons for tooth loss [26]. Periodontitis results in a host immuno-inflammatory response in periodontal tissues caused by periodontal bacteria [27] and viruses [28], and is responsible for pocket formation, attachment loss and bone loss.

It affects 47 % of adults aged 30 and older in the U.S [29], whereas severe PD has affected 743 million people worldwide, its prevalence has been assessed to be 90%, whereas its prevalence and severity increases with age [30]. Oral condition may influence systemic health [31] as a relationship between PD and systemic diseases such as cardiovascular disease [31, 32], type 2 diabetes mellitus [31], rheumatoid arthritis [33], osteoporosis [31], respiratory diseases, such as COPD [34], and several types of human cancers, has been observed [35].

Chronic inflammation caused by bacterial infection has been considered as one of the main factors underlying the development of cancer. Periodontal infection induces inflammation reactions that may increase the risk of tumor-promoting effects [36]. Pathogenic microorganisms such as *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* result in chronic inflammation and destruction of periodontal tissues [37]. In addition, the spread of oral bacteria and inflammatory mediators and biomarkers from the oral cavity can cause and main-tain systemic inflammatory conditions and damage to various organs [38]. The inflammatory reaction induces, directly or indirectly, cell proliferation, the release of reactive oxygen species (ROS), reactive nitrogen intermediates (*RNI*) and other metabolites that can promote cancer initiation [38, 39]. Specific oral bacteria such as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Tannerella forsythia*, *Treponema denticola*, and *Porphyromonas gingivalis* were positively associated with various types of cancers [40], as are able either to up- or downregulate pro-inflammatory cytokines and chemokines, such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (C-rp), affecting the oral and systemic immune systems and also induce oncogenic responses [41]. Accumulating evidence suggests an hypothesized role of immune-inflammatory mechanisms and the potential role of inflammation in both periodontitis and cancer [42] that may be common to both PD and cancer [43, 44] Previous researches have shown that PD individuals have a greater risk of cancer overall [37, 45-50] and in special systems such as hematopoietic cancers [42, 43, 51, 52]. However, the results of similar studies regarding the association between PD and cancer risk, in general, were conflicting. In case of hematopoietic cancer and the possible association of PD as a risk factor few epidemiological studies have been carried out. Consequently, prospective and retrospective studies are required to further elucidate the association examined. The current investigation is the first in Greece that explored the possible association, as noprevious researches have been carried out. The purpose of the current retrospective case-control study was to investigate the possible association between PD indices and risk of two types of hematopoietic cancer, AML, and ALL in a sample of adults in Greece.

2. Materials and Methods

2.1. Study Population Sample and Design

A retrospective case - control research was carried out between May 2019 and October 2021.The study sample was assessed according to EPITOOLS guidelines (https://epitools.ausvet.com.au) determined with 95% Confidence Interval (CI) and desired power 0.8, whereas the age group was based on the World Health Organization (WHO) recommendations [53] for assessing PD incidence. Consequently, 174 individuals who suffered from AML and ALL-cases and 174 healthy individuals-controls consisted the study sample, aged 47 to 77. *Inclusion/Exclusion Criteria of Cases and Controls* Cases and controls should have more than 20 natural teeth, should not have been operated surgically or conservatively for PD during the last six months or had received a systemic anti-inflammatory or antibiotics prescription or other drugs for systemic diseases or disorders, such as glucocorticoids the previous six weeks. The mentioned exclusion criteria could influence [54] the oral tissues status, and may result in biased secondary associations. Advanced AML and ALL individuals under medical treatment, or distant metastases were also excluded from the study protocol. AML and ALL individuals diagnosis derived from their medical files with a definitive diagnosis based on bone marrow examination aspiration and biopsy [55] and before the application of any treatment such as chemotherapy, radiation therapy, chemotherapy with stem cell transplant,

and targeted therapy. Control group was consisted of the friendly and collegial environment of cases in an effort to control potential confounders such as age and smoking.

2.2. Questionnaire

Cases and controls completed a questionnaire that contained epidemiological parameters such as age, gender, smoking status, past medical/dental history, and some parameters that they have been considered as AML and ALL risk factors.The intra-examiner variance was established after clinical re-examination of a randomly selected sample of 70 (20%) individuals by the same dentist after three weeks, and no differences were recorded between the 1st and the 2nd clinical assessment *(Cohen's Kappa = 0.96*). During this time period no oral hygiene instructions were given to the participants.

2.3. Periodontal Status Examination

Periodontal condition was estimated at six sites in all teeth (disto-buccal, mesio-buccal, mid-buccal, mesio-lingual,disto-lingual and mid-lingual),excluding remaining roots and third molars, using a manual periodontal probe (UNC-15; Hu Friedy Mfg. Co. Inc., Chicago, IL USA). The worst measurements of PPD and CAL on six sites per tooth, and the gingival condition (Gingival Index, GI) were recorded and classified as dichotomous variables for each individual. PPD was coded as 0-3.00 mm (no disease/mild disease) and ≥ 4.0 mm (moderate/severe disease) for mean PPD [56], attachment loss (CAL) severity was coded as mild, 1-2.0mm of attachment loss and moderate/severe, ≥3.0 mm of attachment loss [57] , and the severity of gingivitis classified as score 0: normal situation of gingival tissue/mild inflammation, insignificant change in colour and oedema, absence of bleeding on probing, which corresponds to Löe [58] classification as score 0 and 1, and -score 1: moderate inflammatory reaction with presence of redness, oedema, glazing and bleeding on probing/severe inflammatory reaction with presence of significant redness, oedema, ulceration and tendency to spontaneous bleeding, which corresponds to Löe classification as score 2 and 3.

2.4. Ethical Consideration

The current retrospective case - control study was not reviewed and approved by authorized committees (Ministry of Health, etc.), as in Greece only experimental studies must be approved by those Authorities. An informed consent form was gotten by the individuals who agreed to take part in the current study protocol.

2.5. Data Statistical Analysis

The worst values of PPD and CAL and the classification of severity of gingival inflammation (GI) were recorded and coded as dichotomous variables for each individual. Male gender, previous/current smokers, individuals with congenital diseases, those with previous chemotherapy/radiotherapy for cancer treatment in other location was coded as 1. Age groups distribution was coded as 0,1,2 and 3 for ages 47-50, 51-60, 61-70, and 71-77 respectively. Chi-square test (univariate analysis model) was performed to analyze the association between the independent variables examined and AML/ALL risk, separately. Logistic regression model was performed to investigate the relationships between the dependent variable, AML/ALL, and independent ones that were determined by the enter method. Unadjusted and Adjusted Odds Ratios (OR's) and 95% CI were also recorded. Finally, the independent variables were included to stepwise method in order to assess gradually the parameters that showed significant associations with the dependent one. SPSS ver.19.0 package was used for the statistical analysis, whereas p-value of less than 5% ($p< 0.05$) was considered significant for all statistical test conducted.

3. Results

The mean age of the sample was 58.6 ± 2.6 years. The epidemiological parameters of AML and ALL patients and controls after performing the univariate analysis are presented in Table 1. Congenital diseases (p=0.037), previous chemotherapy (p=0.031), smoking (p=0.018), CAL (p=0.023), and GI (p=0.000), were statistically significant associated with risk for AML/ALL development. Table 1 also shows Unadjusted OR's and 95% CI for each variable examined. Congenital diseases included Down syndrome (44 individuals), neurofibromatosis type I(6 individuals), and Bloom syndrome (3individuals), for cases, and 30, 4,and 2 individuals, for control group, respectively. Cases that underwent previous radiation exposure included medical diagnostic radiation (15 individuals) in which the risk varies as CT scans, bone scans, and PET scans involving much more radiation than ordinary X-rays, and medical therapeutic radiation for cancer treatment (10 individuals) that can increase the risk of developing leukemia, especially AML, with the risk highest in the period five to nine years after radiation. The risk varies with the site of radiation as well as the dose used [59].

Cases that received chemotherapy included cyclophosphamide (12 individuals), chlorambucil (9 individuals), etoposide (7 individuals), teniposide (4 individuals), lomustine(4 individuals), carmustine (3 individuals), and busulfan (3 individuals), for cases, and cyclophosphamide (8 inividuals), chlorambucil (7 individuals), etoposide (5 individuals), carmustine (4 individuals), andbusulfan (2 individuals), for control group. Table 2 shows the first method(step 1a) of the logistic regression model, Adjusted OR's and 95% CI for each parameter examined. GI (p= 0.055, 95% CI= 2.126, 1.154-3.468) was marginally statistically significant associated with risk for AML/ALL development.The final step of logistic regression analysis model (Wald method) is presented in Table 2, and showed that CAL (p=0.054, 95% CI= 2,467, 1.177-2.231) and GI (p=0.043, 95% CI=3.352,1.285-4.745) were significantly associated with AML/ALL risk.

Table-1. Univariate analysis of cases and controls regarding each independent variable

Variables	Cases	Controls	p-value	Odds Ratio and 95% Confidence Interval
Gender Males Females	 104(59.8) 70(40.2)	 95(54.6) 79(45.4)	0.330	1.235(0.807-1.870)
Age 45-50 51-60 61-70 71+	 30 (17.2) 57 (32.8) 75 (43.1) 12 (6.9)	 38 (21.8) 60 (34.5) 58 (33.3) 18 (10.3)	0.222	_____
Congenital Diseases Absence Presence	 121(69.5) 53 (30.5)	 138 (79.3) 36 (20.7)	**0.037***	1.679 (1.030-2.737)
Previous Chemotherapy No Yes	 132 (75.9) 42 (24.1)	 148 (85.1) 26 (14.9)	**0.031***	0.552 (0.321-0.950)
Previous Radiotherapy No Yes	 149 (85.6) 25 (14.4)	 158 (90.8) 16 (9.2)	0.135	0.604 (0.310-1.175)
Smoking Status Never Smokers Former/Current Smokers	 66 (37.9) 108 (62.1)	 88 (50.6) 86 (49.4)	**0.018***	0.597 (0.390-0.915)
Probing Pocket Depth 0-3.00 mm ≥ 4.0 mm	 73 (42.0) 101 (58.0)	 84 (48.3) 90 (51.7)	0.236	0.774 (0.507-1.182)
Clinical Attachment Loss 1.00-2.00 mm ≥ 3.0 mm	 64 (36.8) 110 (63.2)	 85 (48.9) 89 (51.1)	**0.023***	0.609 (0.397-0.935)
Gingival Index Absence/Mild Moderate/Severe	 55 (31.6) 119 (68.4)	 93 (53.4) 81 (46.6)	**0.000***	0.403 (0.260-0.623)

* p-value statistically significant

Table-2. Presentation of association between potentially risk factors and AML/ALL according to Enter (first step-1a) and Wald (last step 12a) method of multivariate logistic regression analysis model

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	gender	,149	,417	,128	1	,721	1,161	,513	2,628
	age	,053	,213	,062	1	,804	,949	,625	1,439
	prev.chemo	,205	,525	,153	1	,696	,814	,291	2,278
	prev.radioth	,341	,592	,331	1	,565	1,406	,440	4,489
	smoking.stat	,478	,434	1,210	1	,271	1,612	,689	3,774
	prob.poc.dep	,251	,448	,312	1	,576	1,285	,534	3,093
	clin.att.loss	,954	,531	3,230	1	,072	2,385	1,136	2,090
	ging.index	1,140	,508	5,027	1	**,055***	2,126	1,154	3,468
	Constant	,460	,507	,822	1	,365	1,584		
Step 7[a]	clin.att.loss	,761	,494	2,370	1	**,054***	2,467	1,177	2,231
	ging.index	1,210	,489	6,111	1	**,043***	3,352	1,285	4,745
	Constant	,713	,321	4,932	1	,026	2,040		

a. Variable(s) entered on step 1: gender, age, prev.chemo, prev.radioth, smoking.stat, prob.poc.dep, clin.att.loss, ging.index.

* p-value statistically significant

4. Discussion

The last 50 years the relationship between PD, gingivitis and mainly periodontitis, and cancer risk has been investigated, however, findings to date have little practical value as indices for establishing prevention policies. The current investigation showed that moderate/sever CAL was marginally significant associated with risk of developing AML and ALL, whereas moderate/severe gingival inflammation was significantly associated with the risk examined. Epidemiological parameters such as male gender, and advanced age increase the risk for AML and ALL development [13, 60, 61]. The current report did not confirm the mentioned associations. Individuals that underwent previous chemotherapy and radiotherapy were not at increased risk for developing AML and ALL, findings that were not in line with the outcomes of previous researches [7-14]. Smoking is a known carcinogenesis risk factor and can affect AML risk [10, 13], however the current study did not confirm the

mentioned association. In addition, smoking is a major risk factor for PD [62], and the bacterial microbiota in PD patients differs between smokers and non-smokers [63, 64]. Congenital diseases such as Down and Bloom syndrome, have also been suggested as possible AML risk factors [10, 13]. Similarly, congenital diseases such as Down and Bloom syndrome, and neurofibromatosis type I, are considered as ALL risk factors [20].

The outcomes of the present research recorded no associations between the mentioned diseases and risk of AML/ALL development. The mechanism that is involved in cancer development in PD patients is still remain unclear. An hypothesized role of immune-inflammatory mechanisms and a potential role of inflammation in both periodontitis and cancer has been suggested [42]. The periopathogenic bacteria and their by products associated with chronic periodontitis can result in chronic systemic inflammation [65, 66] not only at the oral tissue but even at distant locations [67]. An accumulation of periodontal pathogens has been detected at local or distant locations, as are able to infiltrate through infected periodontal tissues into the systemic circulation and reach those distant locations [66], such as various organs and tissues including lymph nodes [68], arteries [69, 70] etc. At the target location, periodontal pathogens may promote an appropriate micro-environment that can contribute to cancer progression [71-73]. Inflammation has been identified to act as a cancer hallmark [74], and PD is an infectious process that induces chronic low-grade inflammation and persistent low-grade inflammation has been associated with cancer initiation [39, 75, 76]. Inflammatory response can produce ROS and active intermediates generating oxidative/ nitrosative stress, that may result in DNA mutations, or they may affect the DNA repair mechanisms [77]. The inflammatory cells may further contribute to the cells damage by producing ROS, cytokines, chemokines, and arachidonic acid metabolites. Those products recruit various inflammatory cells and maintain a vicious cycle [77]. Periopathogenic bacteria such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are anaerobic, gram-negative bacteria that colonize sub gingival biofilms in periodontitis patients [78]. Those bacteria produce and release enzymes that deconstruct the extra-cellular matrix components including collagen, process that results in production of substrates that enhance tissue invasion [80]. Those bacterial enzymes, endotoxins, and metabolic by products are toxic to tissues, may cause direct damage to neighboring epithelial cells DNA, and they can induce mutations in protooncogenes and tumor suppressor genes, or cause alterations in molecular signaling pathways implicated in cell survival, proliferation or differentiation [79]. Oral bacteria may promote carcinogenesis by constitutively activating toll-like receptors, such as toll-like receptor 5 (TLR5) [80]. TLR5 are present on the cells surfaces of the innate immune system, have also been associated with epithelial and cancer cells [81] and are involved in inflammation, proliferation, invasion, and anti-tumor immune responses evasion [82, 83]. To bemore specific, previous researches revealed that *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can promote tumor progression by activating TLRs on oral epithelial cells to up-regulate the IL-6/STAT3 signaling pathway [84]. Recently, epidemiological studies have investigated the risk of hematopoietic and lymphatic cancers in individuals with periodontitis [42, 43, 50-52, 85]. However, these studies led to inconsistent results and the evidence remained inclusive. Chung, *et al.* [43] in a population-based study on the associations between chronic periodontitis and the risk of cancer recorded increased risks of hematological cancers combined (HR=1.18, 95% CI=1.02-1.37). A prospective study that examined the PD severity and cancer risk in post-menopausal females using oral alveolar crestal height as PD index, showed that severe PD was associated with a two-fold higher risk of hematological cancers, including leukemia and other hematological cancers (HR=2.09; 95% CI= 0.68, 6.47) [51]. Michaud, *et al.* [42] reported increased risks between PD and hematopoietic malignancies (HR= 1.30, 95%, CI=1.11-1.53). The investigators also observed slightly stronger associations among dentists for PD and hematopoietic cancers (HR = 1.37, 95% CI = 1.12–1.67 among dentists, and HR = 1.22, 95% CI =0.91–1.63 among non-dentist health professionals, respectively). After controlling for smoking and other risk factors, PD was found to be statistically significant associated with an increased risk of hematopoietic cancers, whereas among never smokers, PD was associated with statistically significant increases in hematopoietic cancers (HR = 1.35, 95% CI = 1.01–1.81). Another similar research revealed no association between PD and hematopoietic malignancies in the overall population [HR=1.11, 95%CI= 0.95-1.30], however was statistically significant when limited to never-smokers [HR= 1.34, 95% CI= 1.08-1.67]. Especially in case of leukemias no association was observed (HR=1.10, 95% CI= 0.83-1.47) [52]. In a recent research, in which PPD and gingival recession were used to define PD severity, no associations were observed between those indices and hematopoietic and lymphatic cancers combined (HR=0.89, 95% CI=0.52-1.52) [50]. Another nationwide study in Taiwan also recorded no association between periodontitis and hematological cancers [85]. Various underlying mechanisms have been suggested for the potential association. PD may increase cancer risk through the chronic release of inflammatory mediators or immune system dys regulation [39, 86-88], or may affect carcinogenesis through the increased exposure to carcinogenic nitrosamines [89]. The production of oral bacteria and nitrosamines is increased in oral cavity in individuals with poor oral hygiene and PD [90]. Consequently, anti-inflammation therapy in PD individuals reduces the systemic inflammation biomarkers and may decrease subsequent cancer risk. On the contrary, a report carried out by Hwang, *et al.* [91] recorded that anti-inflammation treatment did not reduce the lymphatic and hematopoietic cancers risk. Tooth loss is another index of advanced periodontitis as tooth loss is often the result of severe periodontitis and was found to be positively associated with risk of certain cancers such as head and neck, esophageal, and lung cancers [90]. Moreover, a dose response meta-analysis revealed that each tentooth loss was associated with a 3% increase of risk of hematopoietic cancer [92]. As shown, few previous and recent reports have observed an increased riskof AML/ALL development among individuals with PD however, notable limitations of those included inadequate sample sizes and inadequate adjustment for potential confounders.

The strengths and limitations of the current research should be taken into account in interpreta-tion of the observed outcomes. Strengths of the study are the completeness of follow-up, the well -characterized cohort that it

was possible to examine both confounding and interaction by known risk factors, in order to avoid secondary biased associations. Another crucial aspect is PD determination by oral clinical examination and not by self-report, thus no possible misclassification of exposure to PD exists that may lead to the underestimation of the association examined. A potential limitation is the possibility of confounding in estimates of risk caused by additional unknown confounders.

5. Conclusion

Individuals with moderate/severe CAL and moderate/severe gingival inflammation (GI) were marginally significantly associated and significantly associated, respectively, with an increased risk of developing acute hematopoietic cancer.

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Cover Letter

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