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Exhaled Volatile Organic Compounds in Patients with a Medical History of Cancer/Dysplasia

Donatini B* and Le Blaye I

Medicine Information Formation (Research), Cormontreuil, France

***Corresponding author:** Donatini B, Gastroenterology-Hepatology, Medicine Information Formation (Research), 40 rue du Dr Roux, 51350 Cormontreuil, France, Tel: E-mail: donatini@orange.fr

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Abstract

Background: Exhaled Volatile Organic Compounds (E-VOCs) have been associated with cancer and may help to early detection or even identify pre-cancerous status.

Objective: We investigated whether a new ambulatory device is able to detect specific E-VOCs in patients with a medical history of cancer or dysplastic lesions and to which medical conditions they are associated.

Methods: All data were collected during routine consultations for Small Intestinal Bowel Overgrowth (SIBO). A breath test was performed by X-PID 9500®.

Results: 650 patients were included. 133 patients reported cancer or dysplasia. Three medical statuses associated with cancer/dysplasia were identified: TH1-immunosuppression, tissue destruction or vagal impairment.

Patients of the cancer/dysplasia group exhale more frequently specific E-VOCs (cluster 58 to 74.9s), especially for digestive lesions. The sensitivity of the E-VOCs cluster 58 to 74.9s to identify patients with a medical history of digestive cancer or dysplastic lesions is 95.0%. The specificity is 82.8%. The positive predictive value is 43.7% and the negative predictive value is 99.2%.

We hypothesized that the cluster 58 to 74.9s could be an early marker of local tissue alteration entangling the three above-mentioned mechanisms.

Conclusion: X-pid 9500® is able to detect E-VOCs associated with cancer/dysplasia in ambulatory practice. Further studies are necessary to investigate the type and the localisation of the implicated dysbiosis as well as the influence of the diet on these E-VOCs.

Keywords: Breath test; Cancer; Chromatography

List of abbreviations: CMV: Cytomegalovirus; COVID-19: Coronavirus Disease; EMT: Epithelial Mesenchymal Transition; E-VOCs: Exhaled Volatile Organic Compounds; FN: *Fusobacterium nucleatum*; HPV: Human papillomavirus; HRV: Heart Rate Variability; LMW-HA: Low Molecular Weight Hyaluronic Acid; NPV: Negative predictive value; PPV: Positive predictive value; RT: Retention time; Se: sensitivity; SIBO: Small Intestinal Bowel Overgrowth; Sp: Specificity; UC: Ulcerative Colitis

Introduction

Imbalanced intestinal microbiota may favour chronic inflammation/destruction of mucosa, vagal impairment, as well as decreased immunity [1,2]. Regarding the latter point, gut microbiota may impact for example the efficacy of checkpoint inhibitors in anti-cancer immunotherapy [3-5] or the occurrence of mild Coronavirus Disease (COVID-19) [6].

Intestinal microbiota can be studied by the analysis of exhaled gases such as hydrogen or methane [7-10].

Many authors reported links between specific exhaled volatile organic compounds (E-VOCs) and cancers [11,12], especially for breast [13,14], digestive tract [15-18] or prostate [19].

Specific E-VOCs are possibly related to gut-TH1-immunosuppression and consequently may favour opportunistic infections such as mild COVID-19 [6]. Hindered TH1-immunity or excess of T-regulators favours the occurrence of cancers, especially those virus-related (like human-papillomavirus (HPV)-induced cervix epithelioma) [20] or adenocarcinoma of the gut [21].

Altered oral or gut microbiota may be responsible for chronic mucosal inflammation and destruction. For example, *Fusobacterium nucleatum* (FN) proliferation may impair mucosal barrier or gut immunity, and induce molecular alterations [22]. FN has been implicated in periodontitis [23], ulcerative colitis (UC) [24,25] or colonic adenocarcinoma [26,27]. FN may eventually trigger

Epithelial-Mesenchymal Transition (EMT) and therefore promote the transformation of colitis into dysplastic mucosa [28]. In animal models, E-VOCs in the urine may varie according to EMT or a specific EMT-associated environment [29].

Nickel allergy should also be considered as a cause of mucosal damage [30].

E-VOCs may be a marker of destruction or inflammation itself rather than a marker of cancer *per se* [31,32]. E-VOCs may therefore precede the occurrence of dysplasia and may detect early predisposing medical or physiological conditions.

Eventually, neuroimmunomodulation and the role of the vagus nerve in cancer have recently been emphasized [33-36]. E-VOCs may also be the consequence of altered gastro-intestinal voiding.

We investigated whether a specific E-VOC or a range of E-VOCs detected with a new ambulatory device (X-PID- 9500) was associated with a medical history of cancer or documented dysplasia. We also investigated whether arguments collected in an ambulatory ward were rather in favour of immunosuppression, tissu destruction or altered vagal tone.

We collected data which may be related to: 1) TH1-immunosuppression (opportunistic infections such as herpetic flares, IgG against cytomegalovirus (CMV) or mild COVID-19, 2) destruction of tissues (increased serum low-molecular-weight hyaluronic acid (LMW-HA), periodontitis, ulcerative colitis, or nickel allergy), 3) vagal impairment (gastroparesia, arrhythmia, osteopenia, and depression).

Heart rate variability (HRV) is a recognized marker of vagal tone [37,38]. Gastric emptying correlates with HRV [39]. Abdominal ultrasound is routinely performed in all patients coming for SIBO. We took advantage of the ultrasound examination to investigate gastric, jejunal and ileal movements [40,41].

Material and methods

This work is a descriptive retrospective epidemiological study.

Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth (SIBO), from 2020 March 1st to 2020 September 30th.

There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before the work has already been done. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE).

Inclusion criteria

Patients consulting for SIBO and who underwent a breath test. Patients should provide with a full medical history, especially regarding cancer and precancerous lesions, herpes simplex, herpes zoster, periodontitis, nickel intolerance, ulcerative colitis, depression, thyroid pathologies, auto-immune diseases, allergic reactions, arrhythmia, depression, osteoporosis, body weight and height, as well as diabetes mellitus.

CMV serology, serum hyaluronic acid titration and transabdominal plus thyroid ultrasound examinations are routinely performed in patients consulting for SIBO.

Patients signed a written consent for the possible retrospective use of the collected data.

Exclusion criteria

Ongoing tobacco abuse (which may interfere with E-VOCs); lack of CMV serology or of hyaluronic acid analysis; lack of transabdominal ultrasound; lack of signed consent for possible retrospective epidemiological use of data; uncontrolled diabetes mellitus; lack of breath test or recent intake of antibiotic therapy or of essential oils leading to massive destruction of the digestive flora and less than 2 ppm of E-VOCs at the first measure, after 10 hours of fasting; uncontrolled endocrine disease (including thyroid insufficiency); incomplete data on drug or food complement intake.

Medical history of cancer or precancerous lesions

All type of cancer or dysplasia were included. Lesions should have been histologically documented. As a consequence, non-dysplastic polyps were not included in the cancer group. Gallbladder polyps diagnosed by ultrasound examination were therefore not graded as dysplastic polyps.

Ultrasound examination

Gastroparesis was diagnosed when the surface of the stomach reached 10 cm^2 after 10 hours of fasting. Ileal distension was diagnosed as soon as ileal diameter reached 2.2 cm at the ileocecal junction. Lack of gastro-duodenal voiding was diagnosed when no evacuation of bubbles between the superior mesenteric artery and the aorta was observed after 2 minutes of osteopathic

abdominal manoeuvers. Jejunal hypotonia could also be implicated. In that case, the jejunum contains few bubbles and no peristalsis is visualized [40,41]. Abdominal ultrasound examination also enables to diagnose liver steatosis.

Gas measurement

The patient comes after at least 10 hours of fasting. He /she inhales room air and hold his/her breath for 20 seconds. He/she exhales the air of the lungs in a first neutral plastic bag (1.3 litre) and afterwards he/she exhales at least 100 ml (expected to belong to the expiratory reserve volume) in a small neutral plastic bag (Contralco®; Gignac; France; www.contralco.com).

E-VOCs from the second bag are then immediately measured by the X-pid 9500®, an ambulatory gas chromatograph associated with photoionization detection technology [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors]. X-pid 9500® detects Volatile Organic Compounds (VOCs) concentrations as low as 50 ppb. Isobutylene and methylacetate are detected within 5.6 to 6.4 seconds, isobutyric, butyric and acetic acids between 7.0 and 7.9 seconds, toluene between 42 and 44 seconds, m-xylene or p-xylene between 90 and 97 seconds and o-xylene around 115 seconds.

X-pid 9500® does not detect hydrogen and is therefore not suitable for the detection of SIBO related to sugar-malabsorption. X-pid 9500® was used after breath holding and only after fasting, not after sugar intake.

The air of the first bag is analysed by the Dräger X-am® 8000. We routinely use the Dräger X-am® 8000 [Dräger; Lubeck; Germany; www.draeger.com › Products › Multi-Gas-Detectors] to measure hydrogen before and two hours after the intake of lactulose in order to diagnose SIBO related to sugar-malabsorption. Results will be published separately.

Both devices are easily portable and equipped with powerful pumps. Patients could be placed in separate rooms when necessary. The setup is basic and similar for both devices. It requires only a short neutral tube to connect the bag and the device.

The results are quantified and directly exported in Excel tables.

Statistics

Comparisons of percentages or means used two-sample t-tests. Yates correction was used for small samples.

Cancer group and control group were compared for clinical parameters and E-VOCs. Since peaks of E-VOCs may be numerous, we looked for clusters. A cluster contains several E-VOCs with close retention times and which are separated from other clusters by at least 1 second of retention time. A cluster is therefore a group of E-VOCs within a specific range of retention time, separated from other clusters and without overlapping.

Since E-VOCs and clinical diseases could be associated, additional comparisons of subgroups could be performed to identify dependent and independent variables. Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to $p<0.01$.

Sensitivity, false positive ratio, negative predictive value and positive predictive value were calculated for the most relevant E-VOCs cluster.

Control group

All consulting patients were pre-included in the study and no case was discarded except when at least one exclusion criteria was identified. As a consequence no recruitment or selection bias is expected. The control group is equal to the total number of included patients minus the cancer group.

Classical demographic data will be compared. The control group appears appropriate.

Results

This descriptive epidemiological study includes 650 patients.

Organs	Type of lesions	Number of cases* 137 cases: 48 cancers and 89 dysplasia for 133 patients
Digestive tract	Dysplastic colorectal polyps	66
	Colorectal cancer	3
	Stomach	3
	Pancreas	3
	Ulcerative colitis with dysplasia	3
	Cholangiocarcinoma	1
	Barret syndrome with dysplasia	1
Breast	Infiltrating ductal cancer	19
	Lobular cancer with mucin-secreting signet-ring cells	1
	Infiltrating cancer, BCRA2+	1

Organs	Type of lesions	Number of cases* 137 cases: 48 cancers and 89 dysplasia for 133 patients
Cervix or vulva	HPV-related dysplasia Cervix Vulva	 17 2
prostate	Adenocarcinoma	4
Ovary	Adenocarcinoma	3
Endometria	Adenocarcinoma	2
Myeloma		2
Others**		6

* 4 patients experienced 2 types of lesions

** others: bladder, vagina, thyroid, melanoma, liposarcoma and gastrointestinal stromal tumour

Table 1: Details of the 137 reports of cancers or dysplasia

133 patients have a medical history of cancer or dysplasia (cancer group). Four patients experienced two types of lesions. Most cancerous events concerned digestive tract, breast or were HPV-related. Details are provided in Table 1. Please note that gallbladder polyps (13 cases) were not included in the cancer group since dysplasia was not histologically documented.

The descriptive demographic data are summarized in Table 2. The control group contain all patients without cancer or dysplasia and includes patients with gallbladder polyps.

	Cancer group 133 patients	Control Group 517 patients	P values
Females % (number of cases)	74.4% (99)	65.4% (338)	>0.05
Age (years) Mean+/- standard deviation	54.6 +/- 12.5	49.7 +/- 15.5	<0.001
Body Mass Index Mean+/- standard deviation	22.2 +/- 4.01	23.2 +/- 4.36	>0.01

Table 2: Descriptive demographic data of the 650 included patients, according to cancer group (133 patients) and control group (517 patients)

Patients in the cancer group were older (however less than 5 years of age) than in the control group. Body Mass Indexes were similar.

Cancer/dysplasia was more frequently associated with: 1) TH1-immunosuppression such as opportunistic infections (Mild COVID-19 infection or CMV IgG+), 2) tissue destruction (nickel intolerance, ulcerative colitis), 3) vagal impairment (osteopenia, gastroparesis or depression): Respectively: 7.5% versus 3.1% (p<0.001), 19.5% versus 12.8% (<0.001), 8.3% versus 3.7% (<0.001), 12.0% versus 5.0% (p<0.001), 9.8% versus 5.8% (<0.001), 20.3% versus 15.9% (p<0.001) and 15.0% versus 9.3% (p<0.001). Serum LMW-HA level was higher in cancer/dysplasia group: 62.4 µg/l +/- 29.8 versus 29.9 µg/l +/-13.1 (p<0.001) Table 3.

		Cancer group 133 patients	Control Group 517 patients	P values
TH1-immunosuppression	**Opportunistic Mild Covid-19**	10 (7.5%)	16 (3.1%)	<0.001
	IgG CMV+	26 (19.5%)	66 (12.8%)	<0.001
Destruction of tissues	**Nickel intolerance**	11 (8.3%)	19 (3.7%)	<0.001
	Ulcerative colitis	16 (12.0%)	28 (5.0%)	<0.001
	Serum Hyaluronic acid	62.4 µg/l +/- 29.8	29.9 µg/l +/-13.1	<0.001
Vagal impairment	**Osteopenia**	13 (9.8%)	30 (5.8%)	<0.001
	Gastroparesis	27 (20.3)	82 (15.9%)	<0.001
	Depressive mood	20 (15.0%)	48 (9.3%)	<0.001

Table 3: Relevant clinical differences between the cancer group and the control group

The cancer group and the control group did not differ regarding other clinical parameters, especially for arrhythmia Table 4.

Glycaemia was similar in both groups (5.1 +/- 0.6 versus 5.3 +/- 0.9 µmol/l; p>0.05).

	Cancer group 133 patients	Control Group 517 patients	P values
Oral or nasal herpetic flares	64 (48.1%)	211 (40.8%)	>0.02
Allergy	32 (24.1%)	141 (27.3%)	>0.05
Urticaria	16 (12.0%)	50 (9.7%)	>0.05
Thyroid nodules	32 (24.1%)	161 (31.1%)	>0.05
Psoriasis	21 (15.8%)	91 (17.6%)	>0.05
Previous treatment with oral isotretinoin	13 (9.8%)	67 (13.0%)	>0.05
Periodontitis	44 (33.1%)	167 (32.3%)	>0.05
Arrhythmia	8 (6.0%)	45 (8.7%)	>0.05
Rheumatoid arthritis or multiple sclerosis	2 (1.5%)	21 (4.1%)	>0.05
Glycaemia	5.1 +/- 0.6 µmol/l	5.3 +/- 0.9 µmol/l	>0.05
Neutrophil/lymphocyte ratio	1.83 +/- 0.96	1.83 +/- 1.03	>0.05
Eosinophil counts	198 +/- 177 cells/ mm3	178 +/-147 cells/mm3	>0.05

Table 4: Clinical parameters which did not differ between the cancer group and the control group

Neutrophil/lymphocyte ratio or eosinophil counts were normal in both groups: respectively 1.83 +/- 0.96 versus 1.83 +/- 1.03 and 198 +/- 177 cells/mm3 versus 178 +/-147.

Eight clusters of E-VOCs were identified: E-VOCs with retention time (RT) <42s; E-VOCs with RT between 42 and 44.9 seconds; E-VOCs with RT between 45 and 57.9s; E-VOCs with RT between 58 and 74.9s (cluster 58 to 74.9; including butyl acetate), E-VOCs with RT between 75 and 84.9s, E-VOCs with RT between 85 and 89.9s, E-VOCs with RT between 90 and 97s and E-VOCs with RT above 97s.

Cluster 58 to 74.9s, cluster 75 to 84.9, cluster 85 to 89.9s, cluster 90 to 97s and cluster above 97s were more frequently detected in the cancer group. Respectively: 84.2% versus 14.1%, 28.6% versus 17.6%; 10.5% versus 4.2%, 27.8% versus 16.4% and 48.9% versus 34.0% ($p<0.001$) Table 5.

	Cancer group 133 patients	Control Group 517 patients	P values
RT <42s	60 (45.1%)	287 (55.5%)	>0.05
RT between 42 and 44.9s	6 (4.5%)	24 (4.6%)	>0.05
RT between 45 and 57.9s	42 (31.6%)	155 (30.0%)	>0.05
RT between 58 and 74.9s	112 (84.2%)	73 (14.1%)	<0.001
RT between 75 and 84.9s	38 (28.6%)	91 (17.6%)	<0.001
RT between 85 and 89.9s	14 (10.5%)	22 (4.2%)	<0.001
RT between 90 and 97s	37 (27.8%)	85 (16.4%)	<0.001
RT>97s	65 (48.9%)	176 (34.0%)	<0.001

Table 5: Comparison of occurrence of E-VOCs in the Cancer group versus the control group

Cluster 58 to 74.9s appears particularly interesting.

	Cancer group		Control Group		P values
	Number of patients	Number (Percentage) with cluster 58 to 74.9s	Number of patients	Number (Percentage) with cluster 58 to 74.9s	
Digestive tract	80	76 (95%)	570	109 (19.1%)	<0.001
Breast	19	14 (73.7%)	631	171 (27.1%)	<0.001
HPV-related	19	13 (68.4%)	631	172 (27.3%)	<0.001
All cancers/dysplasia	133	112 (84.2%)	517	73 (14.1%)	<0.001

Table 6: Percentages of the three main types of cancer/dysplasia according to cluster 58 to 74.9s

We investigated the relevance of the cluster 58 to 74.9s for patients with digestive cancer/dysplasia, with breast cancers (only infiltrating ductal cancer not BCRA+), or with HPV-related dysplasia Table 6.

The sensitivity of the VOCs cluster 58 to 74.9s to identify patients with a medical history of cancer or dysplastic lesions is 84.2%. The specificity is 85.9%. The positive predictive value is 60.5% and the negative predictive value is 95.5% Table 7.

Diseases		Number of patients	Cluster 58 to 74.9s	Control group	Se§ Sp PPV NPV
All cancers/dysplasia	Yes	133	112 (a)	21 (c)	84.2% 85.9% 60.5% 95.5%
	No	517	73 (b)	444 (d)	
Digestive cancer/dysplasia	Yes	80	76 (a)	4 (c)	95.0% 82.8% 43.7% 99.2%
	No	570	109 (b)	461 (d)	
Breast cancer	Yes	19	14 (a)	5 (c)	73.7% 72.9% 7.6% 98.9%
	No	631	171 (b)	460 (d)	
HPV-induced dysplasia	Yes	19	15 (a)	4 (c)	78.9% 73.1% 8.1% 99.1%
	No	631	170 (b)	461 (d)	
Digestive cancer/dysplasia in patients without arrhythmia	Yes	76	73 (a)	3 (c)	96.1% 87.4% 52.5% 99.3%
	No	522	66 (b)	456 (d)	

§ Se=a/(a+c); Sp=d/(b+d); PPV=(Se*prevalence)/(Se*prevalence+(1-prevalence)*(1-Sp)); NPV=Sp*(1-prevalence)/(Sp*(1-prevalence)+prevalence*(1-Se)); prevalence=(a+c)/(a+b+c+d)

Table 7: Sensitivity (Se), Specificity (Sp), Positive predictive values (PPV), Negative predictive values (NPV) of VOCs 58 to 74.9s for patients with cancer/dysplasia, digestive cancer/dysplasia, breast cancer, HPV-induced dysplasia or for the subgroup of patients with digestive cancer/dysplasia and without arrhythmia

The sensitivity of the VOCs cluster 58 to 74.9s to identify patients with a medical history of digestive cancer or dysplastic lesions is 95.0%. The specificity is 82.8%. The positive predictive value is 43.7% and the negative predictive value is 99.2%.

The sensitivity of the VOCs cluster 58 to 74.9s to identify patients with a medical history of breast cancer is 73.7%. The specificity is 72.9%. The positive predictive value is 7.6% and the negative predictive value is 98.9%.

The sensitivity of the VOCs cluster 58 to 74.9s to identify patients with a medical history of HPV-related dysplasia is 78.9%. The specificity is 73.1%. The positive predictive value is 8.1% and the negative predictive value is 99.1% Table 8.

	Cancer/dysplasia group		Control Group		P values
	Number of patients	LMW-HA levels	Number of patients	LMW-HA levels	
Digestive tract	80	66.5 µg/l +/- 27.4	570	32.3 µg/l +/- 15.0	<0.001
Breast	19	61.8 µg/l +/- 30.0	631	35.8 µg/l +/- 16.1; p<0.001	<0.001
HPV-related	19	48.3 µg/l +/- 36.2	631	36.2 µg/l +/- 15.9	>0.05
All cancers/dysplasia	133	62.4 µg/l +/- 29.8	517	29.9 µg/l +/-13.1	<0.001

Table 8: Serum LMW-HA levels according to the type of cancer/dysplasia or in control group

Serum LMW-HA level was increased in the digestive cancer/dysplasia group (66.5 µg/l +/- 27.4 versus 32.3 µg/l +/- 15.0; p<0.001).

Serum LMW-HA level was increased in the breast cancer group (61.8 µg/l +/- 30.0 versus 35.8 µg/l +/- 16.1; p<0.001).

Serum LMW-HA level was not increased in the HPV-related group (48.3 µg/l +/- 36.2 versus 36.2 µg/l +/- 15.9; NS) Table 8.

We investigated whether cluster 58 to 74.9s was associated with other medical status than cancer/dysplasia Table 9.

	Cluster 58 to 74.9s 185 patients	Control group 465 patients	P values
Arrhythmia	48 (26.5%)	4 (0.65%)	<0.001
Gastroparesis	41 (21.8%)	68 (14.7%)	<0.001
Opportunistic COVID-19	15 (8.0%)	11 (2.4%)	<0.001
Nickel intolerance	14 (7.4%)	16 (3.5%)	<0.001
UC	19 (9.6%)	28 (5.2%)	<0.001
Osteopenia	16 (8.5%)	27 (5.8%)	<0.001
Depressive mood	27 (14.4%)	41 (8.9%)	<0.001
Serum Hyaluronic acid	31.4 µg/l +/- 13.0	38.6 µg/l +/-17.9	>0.05
Autoimmunity **Thyroiditis** **Psoriasis**	 45 (24.3%) 35 (18.9%)	 148 (31.8%) 77 (16.6%)	 <0.01; >0.001 >0.05
IgG CMV+	31 (16.5%)	61 (13.2%	<0.01; >0.001

Table 9: Serum LMW-HA levels, arrhythmia, gastroparesis, autoimmunity, osteopenia, depressive mood, COVID-19 infection, nickel intolerance, IgG CMV+ or UC according to cluster 58 to 74.9s

Cluster 58 to 74.9s was not correlated with serum hyaluronic acid levels.

Cluster 58 to 74.9s was associated with the same medical conditions as cancer/dysplasia, except for vagal impairment, and especially arrhythmia. Arrhythmia without cancer/dysplasia may therefore lead to false positive results regarding cancer detection.

When patients with arrhythmia (52 patients) are excluded from the analysis, the sensitivity of the VOCs cluster 58 to 74.9s to identify patients with a medical history of digestive cancer or dysplasia raised to 96.1%, the specificity to 87.4%, the positive predictive value to 52.5% and the negative predictive value to 99.3% Table 7.

We checked whether or not age (Table 10) and gender (Table 11) have an influence on relevant clinical parameters, especially on the cluster 58 to 74.9s. The median age of the cohort is 52 years of age.

	Age above or equal to 52 years of age 321 patients	Age below 52 years of age 329 patients	P values
Gastroparesis	71 (22.1%)	38 (11.6%)	<0.001
Osteopenia	37 (11.5%)	6 (1.8%)	<0.001
Depressive mood	39 (12.2%)	29 (8.8%)	<0.001
Arrhythmia	33 (10.3%)	19 (5.8%)	<0.001
IgG CMV+	53 (16.5%)	39 (11.9%)	<0.001
All cancers/dysplasia	90 (28.0%)	63 (19.1%)	<0.001
Cluster 58 to 74.9s	101 (31.5%)	84 (25.5%)	<0.01; >0.001
Digestive cancer or dysplasia	39 (12.1%)	41 (12.5%)	>0.05
Nickel intolerance	16 (5.0%)	14 (4.3%)	>0.05
Ulcerative colitis*	4 (1.2%)	38 (11.6%)	<0.001
Opportunistic Mild COVID-19*	11 (3.4%)	15 (4.6%)	<0.001

* Inversely correlated

Table 10: Relevant clinical status and cluster 58 to 74.9s between patients above 52 years of age and below 52

	Female patients 437 patients	Male patients 213 patients	P values
Osteopenia	42 (9.6%)	1 (0.5%)	<0.001
Depressive mood	50 (11.4%)	18 (8.5%)	<0.001
Nickel intolerance	29 (6.6%)	1 (0.5%)	<0.001
All cancers/dysplasia	114 (26.1%)	39 (18.3%)	<0.001
Cluster 58 to 74.9s	136 (31.1%)	49 (23.0%)	<0.001

	Female patients 437 patients	Male patients 213 patients	P values
Gastroparesis	67 (15.3%)	42 (19.7%)	<0.01; >0.001
IgG CMV+	67 (15.3%)	25 (11.7%)	<0.01; >0.001
Opportunistic Mild COVID-19	16 (3.7%)	10 (4.7%)	<0.01; >0.001
Arrhythmia	37 (8.5%)	15 (7.0%)	<0.03; >0.001
Digestive cancer or dysplasia	53 (12.1%)	27 (12.7%)	>0.05
Ulcerative colitis	28 (6.4%)	14 (6.6%)	>0.05

Table 11: Relevant clinical status and cluster 58 to 74.9s according to gender

Age is mainly associated with vagal impairment: gastroparesis, osteopenia, depressive mood and arrhythmia.

Age or gender has no influence on regarding digestive cancer/dysplasia. Age has little or no influence on the presence of cluster 58 to 74.9s: only a trend is detected.

Age as well as gender is associated with an increased risk of all cancers/dysplasia. Gender has an influence on the presence of cluster 58 to 74.9s. However, the association between cluster 58 to 74.9s and breast cancer or HPV-induced dysplasia should be taken into consideration.

Discussion

Clinical parameters and immunity

As expected, patients with a medical history of cancer/dysplasia were older than those of the control group [42]. However, when patients older than 52 years of age were compared to the group with younger patients, no statistical difference was found regarding digestive cancer/dysplasia. No clinical picture suggestive of TH1-immunosuppression or of tissue destruction was identified. Only vagal impairment, such as gastroparesis, osteopenia, depressive mood or arrhythmia, was clearly age-related.

In French Public Health Authority's recommendations, age above 50 is considered as a major criterion to start screening for colorectal carcinoma [43]. However, there is less than 5 years difference between the cancer/dysplasia group and the control group with a standard deviation close to 14 years. Therefore, aging does not appear to be the most relevant physiological parameter influencing the occurrence of cancer/dysplasia.

Gender is associated with an increased risk of all cancers/dysplasia and has an influence on the presence of cluster 58 to 74.9s. These results may be explained by the fact that female patients experience breast adenocarcinoma or HPV-induced dysplasia which are both associated with cluster 58 to 74.9s.

Only one patient reported a promoting genetic factor: i.e. BCRA2+. Mutations do not appear to be key factors of cancer occurrence in usual medical practice.

Gender percentages, body mass index, glycaemia, neutrophil/lymphocyte ratio or eosinophil counts were similar in both groups.

Allergy, autoimmunity, herpetic flares, periodontitis, or previous treatment with isotretinoin (which has been associated with severe malabsorption [44]) were also not discriminatory parameters.

In this cohort, the most relevant clinical parameters associated with cancer/dysplasia were those which suggest: 1) an underlying immunosuppressive condition (opportunistic COVID-19 infection, IgG CMV+, UC, nickel intolerance), 2) tissue destruction (UC, nickel intolerance, high serum hyaluronic acid levels) or 3) vagal impairment (osteopenia, gastroparesis, and depressive mood).

TH1-immunosuppression; perhaps mainly interferon related

Neutrophil/lymphocyte ratio or eosinophil counts are considered to be reliable marker of immunity, especially in patients with colonic cancer [45-48]. They were normal in both groups. Immunosuppression can therefore not be explained by a decreased number of immune cells.

IFNs play a key role in anticancer immunity [49-51]. Cancerous patients are at increased risk to develop opportunistic infections such as COVID-19 [52].

In this cohort, most of the cancer or precancerous lesions have a digestive origin. The association between interferon, natural killer cell activity and the risk of colorectal neoplasia is well established [53-55].

Interestingly, E-VOCs may contain fatty acids produced by bacteria. Fatty acids are known to interfere with Natural killers functions [56,57].

Interferon-auto-antibodies are frequently induced by CMV infection [58-61], which may explain the link between IgG CMV+ and cancer/dysplasia in this study.

Decreased interferon level may favour nickel intolerance [62].

It is noteworthy that a higher prevalence of nickel intolerance is observed in patients with UC [63].

UC flares are mainly dependant on TH17 cells [64]. Many patients received anti-TNF alpha therapy which may down-regulate TH1 and TH17 status. UC is a well-recognized risk factor of digestive cancer/dysplasia [65,66]. The altered intestinal microflora and metabolic perturbations may be responsible for the development of UC into CRC [67].

We may conclude that patients with opportunistic COVID-19 infection, IgG CMV+, nickel intolerance, treated UC could present with a decreased IFNs level and therefore may be at increased risk cancer/dysplasia.

Cluster 58 to 74.9s may be a marker of TH1-immunosuppression. A role of mucosal destruction (due to inflammatory dysbiosis or reactivation of herpesviridae) in the occurrence TH1-immunosuppression is possible.

Cluster 54 to 74.9s is independent of autoimmunity since Hashimoto thyroiditis or psoriasis is not more frequently reported in these patients.

Multiple sclerosis [68,69] and rheumatoid arthritis [70,71] are at least partly associated with an increased TH1immunity and did not favour the occurrence of cancer/dysplasia. They are not more frequently reported by patients who exhaled cluster 58 to 74.9s.

Autophagy, through the cleaning of inflammatory bacteria or fungi, controls the quality of the digestive microbiota [72]. Consequently autophagy decreases inflammation and excessive apoptosis [73]. A positive feedback by small chain fatty acids produced by bacteria stimulates autophagy [74]. Adequate microbiota enables the efficacy of checkpoint inhibitors [3-5] which triggers apoptosis of cancerous cells without inflammation for normal cells. E-VOCs may be a marker of altered autophagy or altered apoptosis. However, we found no published data on specific E-VOCs associated with PDL-1, PD-1, CTLA-4 or autophagy.

Tissue inflammation/destruction

In a preliminary study, we reported that severe periodontitis is associated with an increased level of LMW-HA, and with an increased risk of adenocarcinoma [75].

LMW-HA is known to increase endothelial permeability, to stimulate receptors of cancer stem cells and to favour cancer cells metastasis. Migration of stem-cells according to LMW-HA gradient has been documented [76-79].

In this retrospective epidemiological study, LMW-HA (the only form of HA to be found in serum) was increased in patients with exhaled cluster 58 to 74.9s as well as with digestive cancer/dysplasia or with breast cancer.

Although increased levels of LMW-HA have been reported in cervix ripening during premature labour [80], we did not find any association between increased LMW-HA levels and cervix dysplasia.

LMW-HA hyperproduction or release could be associated rather with adenocarcinoma than with epithelial cancer.

Celiac-like mucosal atrophy has recently been documented in nickel intolerance [30]. Nickel intolerance may favour UC [63]. UC and nickel intolerance appears to be clinical pictures associated with immunosuppression and mucosal destruction.

Cluster 58 to 74.9s is not associated with increased levels of serum hyaluronic acid. It may rather detect gut-immunosuppression or vagal impairment.

Vagal impairement

Heart rate variability is a key parameter to measure vagal tone [37,38].

Decreased HRV is associated an increased risk of sudden death of cardiovascular origin, including arrhythmia [81,82], and of decreased survival in patients with cancer [83,84]. HRV is decreased in patients with depressive mood [85-87], gastroparesis [39] or osteopenia [88,89].

Arrhythmias do not occur more frequently in the cancer group. However, they were more frequently reported in patients with exhaled cluster 54 to 74.9s. Gastroparesis is also associated with this cluster.

Vagal impairment could explain the occurrence of arrhythmia [90-92] as well as of gastroparesis [93, 94]. Please note that gastroparesis and osteopenia are correlated with age. Vagal impairment increases with aging [95-97] and may explain these results. However arrhythmia was not age-dependent.

In animal experiments, vagal impairment may induce altered-T-regulation leading to colitis [98-100].

An increased level of IL17 may be detected in arrhythmia, however, no increased frequency of decreased level of IFNs has been reported [101,102].

We hypothesized that cluster 54 to 74.9s could be a marker of vagal impairment.

HRV has not been collected in this study performed in an ambulatory gastroenterological ward. Gastric emptying – which is correlated with HRV [39] – was selected as the digestive marker of vagal impairment. However, since vagal dysfunction may be a corner stone for the occurrence of arrhythmia, dysimmunity-induced inflammation/destruction, it appears useful to systematically measure HRV in ambulatory consultation for SIBO.

VOCs or more specifically Cluster 58 to 74.9s has never been reported before in patients with altered-HRV.

Cluster 92 to 97s has been reported with depression [103]. These microbiota-induced VOCs are however rather inducing direct central-nervous system toxicity than a marker of inflammation/destruction of mucosa.

Exhaled VOCs

In this cohort, an association has been found between cluster 58 to 74.9s and cancer/dysplasia. This association increases when only digestive lesions are considered, especially when patients with arrhythmia are excluded.

The sensitivity of the E-VOCs cluster 58 to 74.9s to identify patients without arrhythmia and with a medical history of digestive cancer or dysplasia is 96.1%. The specificity is 87.4%. The positive predictive value is 52.5% and the negative predictive value is 99.3%.

It is noteworthy to point out that the cluster 58 to 74.9s is not associated with an increased in serum hyaluronic acid, and is associated with arrhythmia. Cluster 58 to 74.9s, may hinder vagal function without destruction of mucosal tissues.

Cluster 58 to 74.9s may contain butyl acetate which belongs to exhaled human volatilome and which is used for human presence detection of hidden or entrapped people [104].

To our knowledge, such a gas has never been reported in association with cancer/dysplasia.

This cluster is unlikely related to COVID-19 infection itself [6].

Further analyses are required to investigate whether specific intake of sugars may modify or not this cluster. The delay before the hypothetical modification will also indicate approximatively the localisation of the dysbiosis: stomach, duodenum, jejunum, ileum or caecum.

Conclusion

All relevant clinical variables associated with cancer/dysplasia are associated with TH1-immunosuppression, tissue destruction or vagal impairment. All three conditions appear to be entangled when the diseases come to clinical expression.

The cluster 58 to 74.9s of E-VOCs is associated with cancer/dysplasia, especially of digestive origin. This cluster might be a good marker of gut-TH1-immunosuppression and vagal disturbances. The sensitivity of this cluster to identify patients with a medical history of digestive cancer or dysplastic lesions is 95.0%. The specificity is 82.8%. The positive predictive value is 43.7% and the negative predictive value is 99.2% which is quite performant for a non-expensive, ambulatory device and for a test which requires less than two minutes.

The cluster 58 to 74.9s appears to be rather a marker of severely altered physiological status with long term tissues consequences at the contact of inflammatory agents rather than of cancer per se or of mild-COVID-19 infection per se.

X-PID 9500® may become an ambulatory tool for detection of detection of increased risks of viral infection or cancer.

Further analyses are necessary to investigate where the inflammation associated with the cluster 58 to 74.9s takes place and which type of diet may trigger or abate it.

Acknowledgment(S) and Conflicts of Interest

No conflict of interest to disclose.

References

1. Bonaz B, Bazin T, Pellissier S (2018) The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. Front Neurosci 7: 49. doi.org/10.3389/fnins.2018.00049.

2. Yoo JY, Groer M, Dutra SVO, Sarkar A, McSkimming DI (2020) Gut Microbiota and Immune System Interactions. Microorganisms 8: 1587. doi: 10.3390/microorganisms8101587.

3. Tomela K, Pietrzak B, Schmidt M, Mackiewicz A (2020) The Tumor and Host Immune Signature, and the Gut Microbiota as Predictive Biomarkers for Immune Checkpoint Inhibitor Response in Melanoma Patients. Life (Basel) 10: 219. doi: 10.3390/life10100219.

4. Miller PL, Carson TL (2020) Mechanisms and microbial influences on CTLA-4 and PD-1-based immunotherapy in the treatment of cancer: a narrative review. Gut Pathog 12: 43. doi: 10.1186/s13099-020-00381-6.

5. Daillere R, Routy B, Goubet AG, Cogdill A, Ferrere G, et al. (2020) Elucidating the gut microbiota composition and the bioactivity of immunostimulatory commensals for the optimization of immune checkpoint inhibitors. Oncoimmunology 9: 1794423. doi: 10.1080/2162402X.2020.1794423.

6. Donatini B, Le Blaye I (2020) Volatile Organic Compounds Associated with Mild COVID-19. Annal Cas Rep Rev ACRR-167. doi: 10.30127/2574-5747/ACRR: 1000167.

7. Pimentel M, Kong Y, Park S (2004) IBS subjects with methane on lactulose breath test have lower postprandial serotonin levels than subjects with hydrogen. Dig Dis Sci 49: 84-7. doi: 10.1023/b:ddas.0000011607.24171.c0.

8. de Lacy Costello BP, Ledochowski M, Ratcliffe NM (2013) The importance of methane breath testing: a review. J Breath Res 7: 024001. doi: 10.1088/1752-7155/7/2/024001.

9. Ledochowski M, Widner B, Bair H, Probst T, Fuchs D (2000) Fructose- and sorbitol-reduced diet improves mood and gastrointestinal disturbances in fructose malabsorbers. Scand J Gastroenterol 35: 1048-52. doi: 10.1080/003655200451162.

10. Donatini B (2015) Pullulation bactérienne de l'intestin grêle. Intérêt du test respiratoire à l'hydrogène et au méthane après lactulose. Revue Inist Hegel 5: 92-99. doi.org/10.4267/2042/56632.

11. Oakley-Girvan I, Davis SW (2017) Breath based volatile organic compounds in the detection of breast, lung, and colorectal cancers: A systematic review. Cancer Biomark 21: 29-39. doi: 10.3233/CBM-170177.

12. Hanna GB, Boshier PR, Markar SR, Romano A (2019) Accuracy and Methodologic Challenges of Volatile Organic Compound-Based Exhaled Breath Tests for Cancer Diagnosis: A Systematic Review and Meta-analysis. JAMA Oncol 5: e182815. doi: 10.1001/jamaoncol.2018.2815.

13. Zhang Y, Guo L, Qiu Z, Lv Y, Chen G, et al. (2020) Early diagnosis of breast cancer from exhaled breath by gas chromatography-mass spectrometry (GC/MS) analysis: A prospective cohort study. J Clin Lab Anal. 4: e23526. doi.org/10.1002/jcla.23526.

14. Mangler M, Freitag C, Lanowska M, Staeck O, Schneider A, et al. (2012) Volatile organic compounds (VOCs) in exhaled breath of patients with breast cancer in a clinical setting. Ginekol Pol 83: 730-6.

15. Altomare DF, Picciariello A, Rotelli MT, De Fazio M, Aresta A, et al. (2020) Chemical signature of colorectal cancer: case-control study for profiling the breath print. BJS Open. doi: 10.1002/bjs5.50354.

16. van Keulen KE, Jansen ME, Schrauwen RWM, Kolkman JJ, Siersema PD (2020) Volatile organic compounds in breath can serve as a non-invasive diagnostic biomarker for the detection of advanced adenomas and colorectal cancer. Aliment Pharmacol Ther 51: 334-346. doi: 10.1111/apt.15622.

17. Markar SR, Brodie B, Chin ST, Romano A, Spalding D, et al. (2018) Profile of exhaled-breath volatile organic compounds to diagnose pancreatic cancer. Br J Surg 105: 1493-1500. doi: 10.1002/bjs.10909.

18. Peters Y, Schrauwen RWM, Tan AC, Bogers SK, de Jong B, et al. (2020) Detection of Barrett's oesophagus through exhaled breath using an electronic nose device. Gut 69: 1169-1172. doi: 10.1136/gutjnl-2019-320273.

19. Jiménez-Pacheco A, Salinero-Bachiller M, Iribar MC, López-Luque A, Miján-Ortiz JL, et al. (2018) Furan and p-xylene as candidate biomarkers for prostate cancer. Urol Oncol 36: 243.e21-243.e27. doi: 10.1016/j.urolonc.2017.12.026.

20. Blanco R, Carrillo-Beltrán D, Osorio JC, Calaf GM, Aguayo F (2020) Role of Epstein-Barr Virus and Human Papillomavirus Coinfection in Cervical Cancer: Epidemiology, Mechanisms and Perspectives. Pathogens 9: 685. doi: 10.3390/pathogens9090685.

21. Raghavan S, Quiding-Järbrink M (2011) Regulatory T cells in gastrointestinal tumors. Expert Rev Gastroenterol Hepatol. 5: 489-501. doi: 10.1586/egh.11.44.

22. Nosho K, Sukawa Y, Adachi Y, Ito M, Mitsuhashi K, et al. (2016) Association of Fusobacterium nucleatum with immunity and molecular alterations in colorectal cancer. World J Gastroenterol 22: 557-66. doi: 10.3748/wjg.v22.i2.557.

23. Miralda I, Uriarte SM (2020) Periodontal Pathogens' strategies disarm neutrophils to promote dysregulated inflammation. Mol Oral Microbiol. doi.org/10.1111/omi.12321

24. Bashir A, Miskeen AY, Hazari YM, Asrafuzzaman S, Fazili KM (2016) Fusobacterium nucleatum, inflammation, and immunity: the fire within human gut. Tumour Biol 37: 2805-10. doi: 10.1007/s13277-015-4724-0.

25. Zhang SL, Wang SN, Miao CY (2017) Influence of Microbiota on Intestinal Immune System in Ulcerative Colitis and Its Intervention. Front Immunol. doi. org/10.3389/fimmu.2017.01674.

26. Bartolini I, Risaliti M, Ringressi MN, Melli F, Nannini G, et al. (2020) Role of gut microbiota-immunity axis in patients undergoing surgery for colorectal cancer: Focus on short and long-term outcomes. World J Gastroenterol 26: 2498-2513. doi: 10.3748/wjg.v26.i20.2498.

27. Shang FM, Liu HL (2018) Fusobacterium nucleatum and colorectal cancer: A review. World J Gastrointest Oncol 10: 71-81. doi: 10.4251/wjgo.v10.i3.71.

28. Yu MR, Kim HJ, Park HR (2020) Fusobacterium nucleatum Accelerates the Progression of Colitis-Associated Colorectal Cancer by Promoting EMT. Cancers (Basel) 12: 2728. doi: 10.3390/cancers12102728.

29. Fan Y, Jalali A, Chen A, Zhao X, Liu S, et al. (2020) Skeletal loading regulates breast cancer-associated osteolysis in a loading intensity-dependent fashion. Bone Res 8: 9. doi: 10.1038/s41413-020-0083-6.

30. Borghini R, De Amicis N, Bella A, Greco N, Donato G, et al. (2020) Beneficial Effects of a Low-Nickel Diet on Relapsing IBS-Like and Extraintestinal Symptoms of Celiac Patients during a Proper Gluten-Free Diet: Nickel Allergic Contact Mucositis in Suspected Non-Responsive Celiac Disease. Nutrients 29: 2277. doi: 10.3390/nu12082277.

31. De Vietro N, Aresta A, Rotelli MT, Zambonin C, Lippolis C, et al. (2020) Relationship between cancer tissue derived and exhaled volatile organic compound from colorectal cancer patients. Preliminary results. J Pharm Biomed Anal 180: 113055. doi: 10.1016/j.jpba.2019.113055.

32. Wu RL, Huang L, Zhao HC, Geng XP (2017) Hyaluronic acid in digestive cancers. J Cancer Res Clin Oncol 143: 1-16. doi: 10.3389/fcell.2018.00048.

33. De Couck M, Caers R, Spiegel D, Gidron Y (2018) The Role of the Vagus Nerve in Cancer Prognosis: A Systematic and a Comprehensive Review. J Oncol 2018: 1236787. doi.org/10.1155/2018/1236787.

34. De Couck M, Maréchal R, Moorthamers S, Van Laethem JL, Gidron Y (2016) Vagal nerve activity predicts overall survival in metastatic pancreatic cancer. mediated by inflammation. Cancer Epidemiol 40: 47-51. doi.org/10.1016/j.canep.2015.11.007.

35. Kloter E, Barrueto K, Klein SD, Scholkmann F, Wolf U (2018) Heart Rate Variability as a Prognostic Factor for Cancer Survival – A Systematic Review. Front. Physiol. 9: 623. doi.org/10.3389/fphys.2018.00623.

36. Hu S, Lou J, Zhang Y, Chen P. Low heart rate variability relates to the progression of gastric cancer. World J Surg Oncol 16: 49. doi: 10.1186/s12957-018-1348-z.

37. Vinik AI, Maser RE, Mitchell BD, Freeman R (2003) Diabetic autonomic neuropathy. Diabetes Care 26: 1553-79. doi: 10.2337/diacare.26.5.1553.

38. Dagres N, Hindricks G (2013) Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? Eur Heart J 34: 1964-71. doi: 10.1093/eurheartj/eht109.

39. Guo W J, Yao SK, Zhang YL, Du SY, Wang HF, et al. (2018). Impaired vagal activity to meal in patients with functional dyspepsia and delayed gastric emptying. The Journal of international medical research 46,792–801. doi.org/10.1177/0300060517726442

40. Donatini B (2019) Intérêt de l'échographie abdominale pour l'analyse des vidanges, des reflux et de la tonicité gastro-duodeno-jéjuno-iléale. Hegel 9: 61. doi. org/10.4267/2042/70441.

41. Donatini B (2020) Dysbiose des Darms In: Leitfaden Viszerale Osteopathie, Elsevier, Germany.

42. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. (2017) Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 3: 524-548. doi: 10.1001/jamaoncol.2016.5688.

43. Haute Autorité de Santé. Cancer colorectal : modalités de dépistage et de prévention chez les sujets à risque élevé et très élevé. Mai 2017.

44. Donatini B, Le Blaye I 2018] Severe Acne in Female Patients Treated with Isotretinoin is associated with Dysbiosis and its Consequences. Journal of Clinical and Cosmetic Dermatology 2: dx.doi.org/10.16966/2576-2826.131.

45. Bowen RC, Little N, Harmer JR, Ma J, Mirabelli LG, et al. (2017). Neutrophil-to-lymphocyte ratio as prognostic indicator in gastrointestinal cancers: a systematic review and meta-analysis. Oncotarget 8: 32171–32189. doi: 10.18632/oncotarget.16291.

46. Mizuno H, Yuasa N, Takeuchi E, Miyake H, Nagai H, et al. (2019) Blood cell markers that can predict the long-term outcomes of patients with colorectal cancer. PLoS One 14: e0220579. doi: 10.1371/journal.pone.0220579.

47. Li M, Spakowicz D, Burkart J, Patel S, Husain M, et al. (2019) Change in neutrophil to lymphocyte ratio during immunotherapy treatment is a non-linear predictor of patient outcomes in advanced cancers. J Cancer Res Clin Oncol 145: 2541-2546. doi: 10.1007/s00432-019-02982-4.

48. Wei Y, Zhang X, Wang G, Zhou Y, Luo M, et al. (2018) The impacts of pretreatment circulating eosinophils and basophils on prognosis of stage Ⅱ-Ⅲ colorectal cancer. Asia Pac J Clin Oncol 14: e243-e251. doi: 10.1111/ajco.12871.

49. Greene TT, Jo YR, Zuniga EI (2020) Infection and cancer suppress pDC derived IFN-I. Curr Opin Immunol 66 :114-122. doi: 10.1016/j.coi.2020.08.001.

50. Zitvogel L, Galluzzi L, Kepp O, Smyth MJ, Kroemer G (2015) Type I interferons in anticancer immunity. Nat Rev Immunol 15: 405-14. Doi: 10.1038/nri3845.

51. Müller L, Aigner P, Stoiber D (2017) Type I Interferons and Natural Killer Cell Regulation in Cancer. Front Immunol 8: 304. doi: 10.3389/fimmu.2017.00304.

52. Bakouny Z, Hawley JE, Choueiri TK, Peters S, Rini BI, et al. 2020) COVID-19 and Cancer: Current Challenges and Perspectives. Cancer Cell 1: S1535-6108(20)30492-X. doi: 10.1016/j.ccell.2020.09.018.

53. Jung YS, Kwon MJ, Park DI, Sohn CI, Park JH (2018) Association between natural killer cell activity and the risk of colorectal neoplasia. J Gastroenterol Hepatol 33: 831-836. doi: 10.1111/jgh.14028.

54. Jobin G, Rodriguez-Suarez R, Betito K (2017) Association Between Natural Killer Cell Activity and Colorectal Cancer in High-Risk Subjects Undergoing Colonoscopy. Gastroenterology 153: 980-987. doi: 10.1053/j.gastro.2017.06.009.

55. Reid FSW, Egoroff N, Pockney PG, Smith SR (2020) A systematic scoping review on natural killer cell function in colorectal cancer. Cancer Immunol Immunother. doi: 10.1007/s00262-020-02721-6.

56. Niavarani SR, Lawson C, Bakos O, Boudaud M, Batenchuk C, et al. (2019) Lipid accumulation impairs natural killer cell cytotoxicity and tumor control in the postoperative period. BMC Cancer 19: 823. doi: 10.1186/s12885-019-6045-y.

57. Marino N, German R, Rao X, Simpson E, Liu S, et al. (2020) Upregulation of lipid metabolism genes in the breast prior to cancer diagnosis. NPJ Breast Cancer 6: 50. doi.org/10.1038/s41523-020-00191-8.

58. Valour F, Perpoint T, Sénéchal A, Kong XF, Bustamante J, et al. (2016) Interferon-γ Autoantibodies as Predisposing Factor for Nontuberculous Mycobacterial Infection. Emerg Infect Dis 22:1124-1126. doi: 10.3201/eid2206.151860.

59. Roerden M, Döffinger R, Barcenas-Morales G, Forchhammer S, Döbele S, et al. (2020) Simultaneous disseminated infections with intracellular pathogens: an intriguing case report of adult-onset immunodeficiency with anti-interferon-gamma autoantibodies. BMC Infect Dis 20: 828. doi.org/10.1186/s12879-020-05553-y.

60. Liu Z, Poiret T, Meng Q, Rao M, von Landenberg A, et al. (2018) Epstein-Barr virus- and cytomegalovirus-specific immune response in patients with brain cancer. J Transl Med 16: 182. doi: 10.1186/s12967-018-1557-9.

61. Burbelo PD, Ching KH, Morse CG, Alevizos I, Bayat A, et al. (2013) Altered antibody profiles against common infectious agents in chronic disease. PLoS One 8: e81635. doi.org/10.1371/journal.pone.0081635.

62. Alecu M, Ghyka G, Coman G (1992) Highly active effect of alpha interferon in blocking the cutaneous delayed hypersensitivity. Rom J Intern Med 30: 291-5.

63. Kageyama Y, Shimokawa Y, Kawauchi K, Morimoto M, Aida K, et al. (2020) Higher Prevalence of Nickel and Palladium Hypersensitivity in Patients with Ulcerative Colitis. Int Arch Allergy Immunol 181: 456-461. doi: 10.1159/000506633.

64. Gálvez J (2014) Role of Th17 Cells in the Pathogenesis of Human IBD. ISRN Inflamm 25: 928461. doi: 10.1155/2014/928461.

65. Olén O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, et al. (2020) Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. Lancet 395: 123-131. doi: 10.1016/S0140-6736(19)32545-0.

66. Axelrad JE, Shah SC (2020) Diagnosis and management of inflammatory bowel disease-associated neoplasia: considerations in the modern era. Therap Adv Gastroenterol 6: 1756284820920779. doi: 10.1177/1756284820920779.

67. Tang Q, Cang S, Jiao J, Rong W, Xu H, et al. (2020) Integrated study of metabolomics and gut metabolic activity from ulcerative colitis to colorectal cancer: The combined action of disordered gut microbiota and linoleic acid metabolic pathway might fuel cancer. J Chromatogr A 1629: 461503. doi.org/10.1016/j.chroma.2020.461503.

68. Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L (2020) T Helper Cells: The Modulators of Inflammation in Multiple Sclerosis. Cells 9: 482. doi: 10.3390/cells9020482.

69. Karpus WJ (2020) Cytokines and Chemokines in the Pathogenesis of Experimental Autoimmune Encephalomyelitis. J Immunol 204: 316-326. doi: 10.4049/jimmunol.1900914.

70. Paparo SR (2019) Rheumatoid arthritis and the Th1 chemokine MIG. Clin Ter 170: e472-e477. doi: 10.7417/CT.2019.2178.

71. Chemin K, Gerstner C, Malmström V (2019) Effector Functions of CD4+ T Cells at the Site of Local Autoimmune Inflammation-Lessons From Rheumatoid Arthritis. Front Immunol 10: 353. doi.org/10.3389/fimmu.2019.00353.

72. Yang L, Liu C, Zhao W, He C, Ding J, et al. (2018) Impaired Autophagy in Intestinal Epithelial Cells Alters Gut Microbiota and Host Immune Responses. Applied and environmental microbiology 84: e00880-18. doi.org/10.1128/AEM.00880-18.

73. Messer JS (2017) The cellular autophagy/apoptosis checkpoint during inflammation. Cell Mol Life Sci 74: 1281-96.

74. Zhou C, Li L, Li T, Sun L, Yin J, et al. (2020) SCFAs induce autophagy in intestinal epithelial cells and relieve colitis by stabilizing HIF-1α. J Mol Med (Berl) 98: 1189-202.

75. Donatini B, Brunissen F, Pereira J, Grandchamp M, Flourat A, et al (2018) Exhaled dimethylcyclopropane may predict medical complications in patients with periodontitis. J Clin Case Stu 3: 10.16966/2471-4925.175.

76. Singleton PA (2014) Hyaluronan regulation of endothelial barrier function in cancer. Advances in cancer research 123: 191-209.

77. Petrey AC, de la Motte CA (2014) Hyaluronan, a crucial regulator of inflammation. Frontiers in immunology 5: 101.

78. Zlobec I, Terracciano L, Tornillo L, Günthert U, Vuong T, et al. (2008) Role of RHAMM within the hierarchy of well-established prognostic factors in colorectal cancer. Gut 57: 1413-9.

79. Wu RL, Huang L, Zhao HC, Geng XP (2017) Hyaluronic acid in digestive cancers. J Cancer Res Clin Oncol 143: 1-16.

80. Kishida T, Yabushita H, Wakatsuki A, Zhuo L, Kimata K (2008) Hyaluronan (HA) and serum-derived hyaluronan-associated protein (SHAP)-HA complex as predictive markers of cervical ripening in premature labor. Connect Tissue Res 49: 105-8.

81. Johnston BW, Barrett-Jolley R, Krige A, Welters ID (2020) Heart rate variability: Measurement and emerging use in critical care medicine. J Intensive Care Soc 21: 148-57.

82. Sessa F, Anna V, Messina G, Cibelli G, Monda V, et al. (2018) Heart rate variability as predictive factor for sudden cardiac death. Aging 10: 166-77.

83. De Couck M, Caers R, Spiegel D, Gidron Y (2018) The Role of the Vagus Nerve in Cancer Prognosis: A Systematic and a Comprehensive Review. J Oncol 2018: 1236787.

84. De Couck M, Maréchal R, Moorthamers S, Van Laethem JL, Gidron Y (2016) Vagal nerve activity predicts overall survival in metastatic pancreatic cancer, mediated by inflammation. Cancer Epidemiol 40: 47-51.

85. Schiweck C, Piette D, Berckmans D, Claes S, Vrieze E (2019) Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. Psychol Med 49: 200-11.

86. Balzarotti S, Biassoni F, Colombo B, Ciceri MR (2017) Cardiac vagal control as a marker of emotion regulation in healthy adults: A review. Biol Psychol 130: 54-66.

87. Kidwell M, Ellenbroek BA (2018) Heart and soul: heart rate variability and major depression. Behav Pharmacol 29: 152-64.

88. Tosun A, Doğru MT, Aydn G, Keleş I, Arslan A, et al. (2011) Does autonomic dysfunction exist in postmenopausal osteoporosis? Am J Phys Med Rehabil 90: 1012-9.

89. Kado DM, Lui LY, Cummings SR (2002) Study of Osteoporotic Fractures Research Group. Rapid resting heart rate: a simple and powerful predictor of osteoporotic fractures and mortality in older women. J Am Geriatr Soc 50: 455-60.

90. Wink J, van Delft R, Notenboom RGE, Wouters PF, DeRuiter MC, et al. (2020) Human adult cardiac autonomic innervation: Controversies in anatomical knowledge and relevance for cardiac neuromodulation. Auton Neurosci 227: 102674.

91. Manolis AA, Manolis TA, Apostolopoulos EJ, Apostolaki NE, Melita H, et al. (2020) The role of the autonomic nervous system in cardiac arrhythmias: The neuro-cardiac axis, more foe than friend? Trends Cardiovasc Med S1050-1738(20)30066-9.

92. Linz D, Elliott AD, Hohl M, Malik V, Schotten U, et al. (2019) Role of autonomic nervous system in atrial fibrillation. Int J Cardiol 287: 181-8.

93. Horn CC (2014) The medical implications of gastrointestinal vagal afferent pathways in nausea and vomiting. Curr Pharm Des 20: 2703-12.

94. Mohammad MK, Pepper DJ, Kedar A, Bhaijee F, Familoni B, et al. (2016) Measures of Autonomic Dysfunction in Diabetic and Idiopathic Gastroparesis. Gastroenterology Res 9: 65-9.

95. Walter U, Tsiberidou P (2019) Differential age-, gender-, and side-dependency of vagus, spinal accessory, and phrenic nerve calibers detected with precise ultrasonography measures. Muscle Nerve 59: 486-91.

96. Junior EC, Oliveira FM (2017) Attenuation of vagal modulation with aging: Univariate and bivariate analysis of HRV. Annu Int Conf IEEE Eng Med Biol Soc 2017: 3178-81.

97. Abhishekh HA, Nisarga P, Kisan R, Meghana A, Chandran S, et al. (2013) Influence of age and gender on autonomic regulation of heart. J Clin Monit Comput 27: 259-64.

98. Teratani T, Mikami Y, Nakamoto N, Suzuki T, Harada Y, et al (2020) The liver-brain-gut neural arc maintains the Treg cell niche in the gut. Nature 585: 591-6.

99. Cawthon CR, de La Serre CB (2018) Gut bacteria interaction with vagal afferents. Brain Res 15: 134-9.

100. Di Giovangiulio M, Bosmans G, Meroni E, Stakenborg N, Florens M, et al (2016) Vagotomy affects the development of oral tolerance and increases susceptibility to develop colitis independently of the alpha-7 nicotinic receptor. Mol Med 22: 464-76.

101. Wu N, Xu B, Liu Y, Chen X, Tang H, et al. (2016) Elevated plasma levels of Th17-related cytokines are associated with increased risk of atrial fibrillation. Sci Rep 6: 26543.

102. Nikoo MH, Taghavian SR, Golmoghaddam H, Arandi N, Abdi Ardakani A, et al. (2014) Increased IL-17A in atrial fibrillation correlates with neutrophil to lymphocyte ratio. Iran J Immunol 11: 246-58.

103. Donatini B, Le Blaye I (2020) Ambulatory Detection of Volatile Organic Compounds (VOCs) Associated with Depression. J Clin Case Stu 5: 10.16966/2471-4925.199.

104. Mochalski P, Wiesenhofer H, Allers M, Zimmermann S, Güntner AT, et al. (2018) Monitoring of selected skin- and breath-borne volatile organic compounds emitted from the human body using gas chromatography ion mobility spectrometry (GC-IMS). J Chromatogr B Analyt Technol Biomed Life Sci 1076: 29-34.