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Stomach Cancer and Parabens

Lama Alloujami[1*] and Sophi Barguil[1]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Damascus, Syria.

Authors' contributions

This work was carried out in collaboration between both authors. Author LA as a part of PhD thesis under the supervision of the author SB. Both authors read and approved the final manuscript.

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ABSTRACT

Background and Objectives: Parabens are one of the chemicals used widely in preserving foods and pharmaceutical preparations. Although it was safe for many years, recently it has been proven that its action mimics estrogen in the body when it is linked to its receptors, known as estrogen receptors which are present in many systems of the body and that it may have a link with breast cancer, especially after it was found in samples of breast cancer. As known that estrogen receptors are placed in different areas in the body, including the stomach, therefore it may have a role in cancer formation and development in the stomach.
The purpose of this manuscript is to investigate the presence of Methyl, Ethyl and Propylparaben in stomach cancer in men and women.
Methods: Samples of stomach cancer have been collected immediately after surgery in Al Assad University Hospital and after extracting parabens from samples, they have been analyzed by HPLC / MS in the science faculty at Damascus University.
Results: All samples have the three types of parabens with total mean concentration (22.5 ± 0.4 ng/g).
The concentration of Methylparaben was the highest (8.2 ± 0.3 ng/g) then Propylparaben (7.4 ± 0.4 ng/g) and finally Ethylparaben (6.9 ± 0.2 ng/g).
Conclusion: Because of the presence of parabens in all stomach cancer samples, so more studies must be done to research if parabens may have any effect in the formation of abnormal cells and the formation of cancer in the body systems which have estrogen receptors.

**Corresponding author: E-mail: lamlouj@gmail.com;*

Keywords: Methylparaben; ethylparaben; propylparaben; stomach; cancer.

ABBREVIATIONS

MP : Methylparaben
EP : Ethylparaben
PP : Propylparaben
BHBA : B-Hydroxybenzoic Acid
ER : Estrogen
min : Minute
ng/g : Nanogram/ gram
HPLC/MS : A High-Performance Liquid Chromatography (HPLC) Attached, via a Suitable Interface, to a Mass Spectrometer (MS)

1. INTRODUCTION

There is no doubt that food and drink (especially processed foods) that a person eats have a major role in the occurrence of many diseases, foremost of which is cancer.

Food statistical studies confirmed that approximately 70% of the causes of most cancers are because of the type of people's nutrition [1].

According to Global Cancer Statistics 2018 [2].

Almost 38.4% of men and women may experience cancer in one part of their lives.

Stomach cancer was the fifth most diagnosed cancer in 2018, at 5.7%, which is about a million new cases and is considered to be the third deadly cancer in the world. The proportion of those who die from this disease is about 8.2%. It forms 9.5% of cancer cases in the world [3,4].

Stomach cancer is more prevalent in men compared to women, and this percentage increases with age [2].

In men, stomach cancer is the fourth most common cancer and the seventh most common cancer in women [3,4].

Stomach cancer is characterized by:

It grows slowly as the symptoms often appear only at a later stage, which contributes to poor prognosis, and therefore is often diagnosed in advanced stages of the disease.

Studies indicate that there is a relationship between the type of foods that a person eats and the possibility of developing these types of malignant tumors [5].

Parabens are one of the chemicals widely used in preserving foods, oils, sweets, and chips, as well as it is the most used in pharmaceutical preparations as it works to prevent reproduction and activity of (bacteria, fungi, and yeasts), and has strong effectiveness within a wide PH range.

70-100% of parabens which are taken up orally are absorbed [6].

For more than 60 years Methylparaben was used in food. According to FDA regulation, methylparaben is generally recognized as safe (GRAS) while used as a chemical preservative in foods, with a use limit no longer exceeding 0.1%.

The first absorption of parabens takes place in the intestine, then hydrolysis into Para-hydroxybenzoic acid (PHBA) in the liver, which is excreted in the urine. PHBA was recognized as safe (GRAS), because of its less toxic than the parent compounds and the excretion process usually takes place in 24 hours [7].

Although parabens are rapidly absorbed, metabolized and excreted, only 2% of the amount received via the digestive pathway remains in the cells and is not excreted outside the body, it is believed that the presence of non-metabolized parabens is what causes toxic effects in the body [6,8].

For paraben which is taken orally:

71- 83% is excreted through the urine.

4% excreted through faces.

While 2% of it remains in the cells.

As all kinds of parabens can excretion, without metabolism in urine, this is evidence that parabens taken from a digestive source are not completely metabolized to B-hydroxybenzoic acid (PHBA) [7].

It is believed that the presence of parabens in the body may lead to a cumulative action that stimulates the abnormal proliferation of cells due to their high ability to penetrate the fat cells, especially since parabens have little dissolution in water and high in fat, as this degradation increases with increasing length of the side chain of the ester.

So, entering parabens to the body may lead to an increase in its accumulation in the fatty tissues as a manner similar to those lipophilic pollutants known as cumulative action [9].

Parabens are characterized by an action that mimics estrogen in the body when it is linked to its receptors, and since estrogen receptors are present in many systems of the body, such as the digestive system and breast, therefore it may have a role in cancer incitation in those systems.

Many recent studies suggested that paraben may have a relationship in developing breast cancer due to its estrogen-stimulating action, especially after it was found in samples of breast cancer [9].

Estrogen plays a pivotal role in many vital functions in both genital and non-genital organs, as it can do cell modifications when it binds to its receptors.

Estrogen hormones are found in both women and men. The estrogen receptors (ERs) are divided into two types: (ER-α and ER-β)

ER-β is a type present with high concentrations in non-estrogen-dependent tissues, including the stomach [10].

Thus, estrogen mediates important functions in a variety of systems through its receptors.

The presence of ER-β in the mucous membrane of the digestive system, especially the stomach, enhances its functional role in the proposed proliferation of cancerous cells.

Although there is a lot of controversy and diversity between the results related to the estrogen hormone in the development of stomach cancer, many recent studies indicate that estrogen stimulates the growth of gastric cancer cells [11].

Studies have been conducted to investigate the roles that estrogen and its receptors play in stomach cancer, especially since the incidence of stomach cancer is much higher in men than in women. Epidemiological studies indicate the ratio of gastric cancer prevalence in male to female over the world is 2:1.

Qualitative studies have shown a documented presence of (ER-α) and (ER-β) at the cellular and tissue levels of stomach cancer. These results confirm that these cancerous tissues have estrogen binding sites, thus, they have the same biochemical properties as in breast cancer but its effect on disease progression remains unclear [12,13].

In this paper, we investigated the presence of parabens in stomach cancer samples in men and women.

2. MATERIALS AND METHODS

The samples of stomach cancer were collected from Al Assad University Hospital (general surgery department) immediately after surgery and before it stored in a Formaldehyde solution and stored at (-80°C) in the hospital lab between (2017-2018). After that, parabens were extracted from the samples in the lab, then they had been carried to the science faculty lab at Damascus University to analyzed by HPLC/MS.

All required approvals from the head of Al Assad hospital, the head of the general surgery department, the Ministry of Higher Education, pharmacy faculty and science faculty to do this research (collect and analyze these samples) had been made before work.

2.1 Reagents and Solutions Used in Analysis [9,14]

Ethanol, acetone, and methanol (PRS Panreac, Spain).

Standard chemicals: Methylparaben (MP), Ethylparaben (EP) and Propylparaben (PP). (Roth, Germany). Sampling analysis: HPLC / MS (SHIMADZU LC MS-2020). The single quadrupole mass spectrometer equipped (Quadrupole mass analyzer design) detected both positive ions and negative ions.

Column type C18, 150 mm x 4.6 mm, ID5 (мm).

Macherey-Nagel nucleoside HPLC

The wave length is 254 nm.

The total flow of 1.2000 mL /min

The program time for each injection is 25 min.

Mobile phase: ammonium acetate (mM 15, PH = 4.5) in pump A, acetonitrile in pump B, (t=0 min A 90%, t=15 A40%, t=16 A 90%, t=25 next injection).

Table 1. Parabens standers: HPLC retention times

Stander: 1 µg/ml	HPLC Retention time (min)
Methyl paraben	8.3
Ethyl paraben	10
Propel paraben	11.7

2.2 Parabens Extraction from Studied Samples

Sample (0.5 g) is cut well by a sterile razor blade and homogenize with (6.25 ml Ethanol + 6.25 ml acetone). This mixture is left all night with periodic shaking.

The next day, the mixture is placed in a bench centrifuge at 2500 rpm for 10 min at room temperature, to separate the phases. The floating layer containing parabens is taken and placed in a clean tube while the remaining tumor mass is re-extracted by adding (1.5 ethanol+1.5 ml acetone) and placed in a bench centrifuge at 2500 rpm for 10 min at room temperature. The floating layer which containing parabens is placed in the previous clean tube. The two upper layers dried to get a spot of dry-oily extract containing parabens.

The dry-oily residue was mixed with 6 ml of 70% aqueous methanol and incubate all night at (-20°C). At the next day, we separate the phases by putting the mix in a bench centrifuge at 3200 rpm for 20 min at (4°C), the floating layer which contains parabens is placed in a clean tube. The bottom phase of the oily dry residue is re-extracted again by adding 1 mL of 70% aqueous methanol and put in a bench centrifuge at 3200 rpm for 20 min at (4°C), the separated floating layer which containing parabens was added to the previous floating layer and the two layers were dried in the open air.

The dry samples containing parabens are taken, dissolved in methanol and analyzed by HPLC/MS.

3. RESULTS

Samples were divided into 6 groups, each group had 2 samples and one blank extraction.

The average (Mean), the standard deviation (SD) and the standard error of the mean (SEM) have been calculated for samples.

3.1 Patient's classification

Table 2 show patients have been classified according to age, gender and tumor stage.

Table 2. Classification of stomach cancer patients

Sample	Male/Female	Age	Tumor degree
1	F	59	III
2	F	56	III
3	M	55	III
4	M	65	III
5	M	60	III
6	M	58	III
7	F	59	III
8	M	63	III
9	F	60	III
10	M	61	III
11	M	57	III
12	F	58	III

3.2 Distribution of Stomach Cancer

Table 3 show the distribution of stomach cancer which is 58% in men and 42% in women.

Table 3. Stomach cancer distribution between men and women

Sample	Male	Female
Total of samples=12	7	5
percentage of samples	58%	42%

3.3 Parabens Concentration in Samples

Table 4 show the concentration of parabens ng/g in tumor and blank extraction in each group and the Mean of parabens concentration is shown in Table 5.

Confidence limits of the mean concentration are shown in Table 6.

Table 7 show the highest concentration of methyl, ethyl and propylparaben in the samples of stomach cancer.

4. DISCUSSION

All tumors examined were of stage III. Age of men were between (55-65) years old and women ages were between (56-60) years old. The average old of men was 60 and women were 58 years.

Table 4. The concentration of parabens ng/g from (tumor and blank extraction)

sample	MP tumor	EP tumor	PP tumor	MP blank	EP blank	PP blank	MP tumor minus blank	EP tumor minus blank	PP tumor minus blank
1	7.8	7.4	7.6	0	1.1	0.7	7.8	6.3	6.9
2	9.2	8.1	7.5	0	1.1	0.7	9.2	7.0	6.8
3	8.5	7.4	7.7	0.2	0.4	0.3	8.3	7.0	7.4
4	7.7	7.5	8.8	0.2	0.4	0.3	7.5	7.1	8.5
5	8.1	7.0	6.0	0.5	0.3	0.2	7.6	6.7	5.8
6	7.4	7.5	9.6	0.5	0.3	0.2	6.9	7.2	9.4
7	7.1	7.3	6.1	1	0.6	0.5	6.1	6.7	5.6
8	10.1	6.7	6.9	1	0.6	0.5	9.1	6.1	6.4
9	8.9	8	7.9	0.4	0	1.2	8.5	8.0	6.7
10	9.2	6.3	8.1	0.4	0	1.2	8.8	6.3	6.9
11	8.7	9.5	8.9	0.3	0.9	0	8.4	8.6	8.9
12	10.9	6.5	9.1	0.3	0.9	0	10.6	5.6	9.1
MEAN	8.6	7.4	7.8	0.4	0.6	0.5	8.2	6.9	7.4
SEM	0.3	0.2	0.3	0.1	0.1	0.1	0.3	0.2	0.4
SD	1.1	0.9	1.1	0.3	0.4	0.4	1.2	0.8	1.3

Table 5. Mean concentration of parabens ng/g in stomach cancer

Mean of parabens	MP	EP	PP	Mean of total parabens
Stomach cancer	8.2	6.9	7.4	22.5
SEM	0.3	0.2	0.4	0.4

Table 6. Confidence limits of the mean concentration of parabens ng/g in stomach cancer

Tumor minus blank	Mean	Confidence Limit
MP	8.2	7.5-8.9(95%)
EP	6.9	6.5-7.3(95%)
PP	7.4	6.5-8.2(95%)
Total parabens	22.5	21.6-23.4(95%)

Table 7. The high concentration of parabens ng/g in stomach cancer

Parabens highest concentration	Stomach cancer
MP	10.6
EP	8.6
PP	9.4

According to global statistics in USA and UK Age-specific, rates of incidence is around age 45-49. This is in line with global statistics that confirm that stomach cancer appears over the age of 40, and the average age in men for stomach cancer is 65 [15,16]. The distribution of stomach cancer which is 58% in men and 42% in women. That is, the incidence rate of stomach cancer in men is higher than women. According to the cancer research in the UK, 34% of stomach cancer cases in the UK are in females, and 66% are in males, other research in the USA confirm that the ratio of stomach cancer in men to women is (1.7:1), a possible explanation is probably that the protective effect of estrogen may lower the risk of stomach cancer in women. [15,16].

All studied samples have three types of parabens. The total mean concentration is (22.5±0.4 ng/g).

The concentration of Methylparaben was the highest in the studied samples (8.2 ± 0.3 ng/g) followed by Propylparaben (7.4 ± 0.4 ng/g) and finally Ethylparaben (6.9 ± 0.2 ng/g).

Many studies confirm that Parabens has been detected in urine, serum, breast milk and seminal fluid in addition to its presence in breast cancer samples. Parabens are detected in the urine, also amongst pregnant women and children. Parabens are also found within the human placental tissue and a sturdy correlation among

urinary paraben concentrations of pregnant ladies and their matching in newborn infants suggest the transfer of the compound from the mom to the fetus. In a few studies, parabens levels had been correlated with biomarkers of oxidative DNA damage in pregnant ladies. Although the correlations might be coincidental, it's far nonetheless an opportunity that parabens, even at very low concentrations, influence organism homeostasis [9,17,18].

5. CONCLUSIONS

Because of the presence of parabens in all stomach cancer samples, so more studies must be done to research if parabens may have any effect in the formation of abnormal cells and the formation of cancer in the body systems which have estrogen receptors.

CONSENT

As per international standard or university standard was written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The samples have been taken directly after surgery and before storing it with Formaldehyde solution.

The approval from the head of Al Assad hospital, the head of general surgery department, the Ministry of Higher Education, pharmacy faculty and science faculty to do this research (collect and analyse this samples) have been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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