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POTENTIAL SIGNIFICANCE OF ALIPHATIC POLYAMINES, α-SYNUCLEINS AND HELICOBACTER PYLORI IN DIAGNOSTICS AND PROGNOSIS OF SOME MALIGNANT TUMORS

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Abstract

Polyamines (putrescine, spermidine and spermine) as well as γ- and α-synucleins are currently the subject of a special comprehensive study due to their direct influence on the formation of neoplastic processes.

This review article presents informative data on the role of aliphatic polyamines (putrescine, spermidine, spermine) in the induction of a number of oncological diseases with their localization in the digestive and urinary systems. Aspects related to the synthesis and aggregation of γ-synucleins into malignantly reborn cells have been discussed. The article provides information on the possible prevention of further growth of malignant cells, by inhibiting enzymatic processes responsible for the polyamine synthesis.

In case of prolonged persistence of Helicobacter Pylori in the stomach, an enhanced synthesis of polyamines and cumulation in situ of oligo- and aggregated gamma synucleins occurs in mucous membrane cells. It is possible that all of the abovementioned factors in total directly and/or indirectly have a stimulating effect on the processes of the malignancy of gastric mucosal cells.

The subject of special discussion was the latest literature data, according to which, under the conditions of Helicobacter Pylori persistence in the digestive tract organs, in the gastric mucosal cells an enhanced synthesis of putrescine occurs, high concentrations of which can have a co-carcinogenic effect on normally functioning target cells. From a qualitatively new point of view, the fact of cumulation in malignantly reborn cells of an aggregated gamma synuclein, which was found during Helicobacter Pylori infection, should be considered.

Keywords: *gastric cancer, poliamines, gamma synuclein, Helicobacter Pylori.*

The 45-year studies have revealed modulating effect of polyamines on reparative-proliferative processes in the tissues of various origins in mammals.

Impaired metabolism of polyamines (putrescin, spermidine and spermine) in epithelial and mesenchymal tissues is frequently observed as a provoking factor which causes hyperplastic processes in parenchymal organs as well as in organs of immunogenesis. At the same time, it is a well-known fact, that hyperplastic processes are considered to be the risk factors both for the occurrence of malignant tumors and for the transformation of benign tumors into malignant ones.

Polyamines (putrescine, spermidine and spermine) as well as γ- and α-synucleins are currently the subject of a special comprehensive study due to

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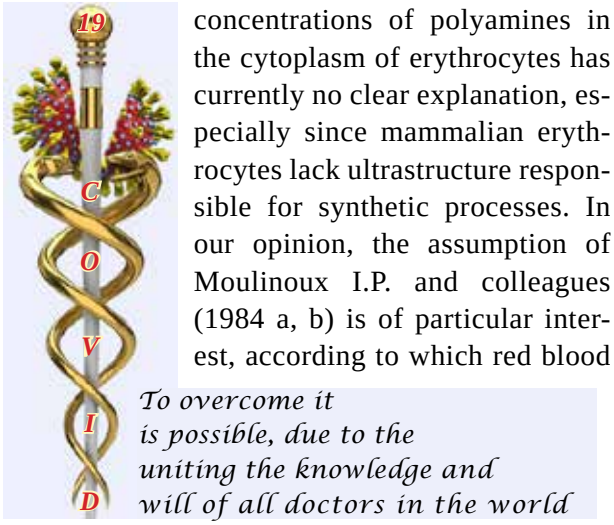
their direct influence on the formation of neoplastic processes. Many advanced scientists began their fundamental researches at the end of the last century [*Volkov N et al., 1983; Jensen J et al., 1987; Moulinoux I, 1989 a, b; Sarhan S et al., 1989; Quemener V, 1990; Seiler N et al., 1990*] having their considerable input in studying the role of polyamines in the pathogenesis of malignant neoplasms. Thus, it was found out that in increased cell proliferation under normal conditions, and especially in malignantly regenerated cells, rather high concentrations of polyamines are determined in their cytoplasm [*Jänne J et al., 1978; Volkov N et al., 1983; Moulinoux I, 1989b; Sarhan S et al., 1989*]. Introduction of polyamines to cell culture medium, where proliferation processes were previously inhibited, markedly restored their mitotic activity. In this regard, in our opinion, the study of Sarhan S. and co-authors (1989), where polyamines from "exogenous" medium are shown to accumulate exclusively in tumor cells, deserves special attention. Equally informative research carried out by Seiler N. and co-authors (1990) revealed that feeding laboratory animals with food deprived of polyamines as well as introducing inhibitors of polyamine biosynthesis into food, significantly inhibits proliferative processes in malignant neoplasms induced in rats.

Particular attention should be paid to the fact that both red blood cells in patients suffering from various malignant diseases and the red blood cells of laboratory animals with induced neoplastic process are characterized by significantly elevated polyamine levels [*Moulinoux I et al., 1984 a,b; 1987*]. The presence of noticeably significant high concentrations of polyamines in the cytoplasm of erythrocytes has currently no clear explanation, especially since mammalian erythrocytes lack ultrastructure responsible for synthetic processes. In our opinion, the assumption of Moulinoux I.P. and colleagues (1984 a, b) is of particular interest, according to which red blood cells characterize the polyamine levels which are released by cancer cells. Meanwhile, Quemener V. (1990) put forward another hypothesis, according to which erythrocytes can act as a "polyamine reserve" for cancer cells in mammals.



The fact that high polyamine content is found not only in cancer cells, but in erythrocytes either suggests broad prospects for both the early diagnosis and prognosis of malignant diseases by studying polyamines in the erythrocytes of patients' blood, since there is a direct correlation between high concentrations of polyamines in cancer cells and red blood cells.

Malignant neoplasms still have the highest rates in morbidity and mortality worldwide. Every year, millions of new cancer cases are recorded all over the world, with the most common being breast cancer, prostate cancer, colorectal cancer, lung cancer, malignant neoplasms of the reproductive organs, etc. According to the summary data of recent years, presented in a review article by Wallace H.M. (2009), the treatment effectiveness of malignant diseases varies significantly, depending on the type of tumor. Thus, with a five-year survival rate for breast cancer, the rate of successful therapy is 80-90%, it makes up 45-55% for colorectal cancer, but is much lower for lung cancer, constituting 5-15%.

As we have indicated above, the new highly informative data appear periodically, indicating the important role of polyamines in the pathogenesis of many malignant diseases. In this regard, certain amendments, concerning the peculiarities of polyamine metabolism and their cumulation in malignantly reborn cells, are accordingly made to the general treatment scheme of oncological diseases (often in the form of "protocols"). Wallace H.M. (2009) who is one of the polyamine theory founders, therein considers four fundamental criteria that should be taken into account when studying various aspects related to the role of polyamines in the induction of cancer: 1. Polyamines are essential for cell growth; 2. The concentration of polyamines increases significantly in malignantly reborn cells; 3. Ornithine decarboxylase should be considered an oncogene (co-oncogene); 4. Interventions, associated with the inhibition of polyamine synthesis prevent the cancer cell growth.

It'd hardly be an exaggeration to say that all the attempts to find new means of symptomatic and

pathogenetic therapy of malignant neoplasms, related to the polyamine metabolism disruption, are based on the tenets mentioned in the paragraphs above.

Polyamine content in malignant human cells is several times higher than in the parent normal cells. In this respect, indicators that are presented in the studies of Kingsnorth A. N. and co-authors (1984 a, b) appear to be very demonstrative. Breast cancer cells thus contain 4-6 times more polyamines than it is found in normal breast cells. A similar pattern is also observed in colon cancer, in which the content of polyamines in malignantly regenerated cells is 3-4 times higher than in normal colon cells. Along with the high level of polyamines in cancer cells, the activity of ornithine decarboxylase, the fundamental enzyme which converts ornithine to putrescine, also increases. High levels of polyamines (putrescine, spermidine and spermine) and high supported liquid membrane activity are observed in certain hyperplastic processes, benign and malignant tumors localized in the organs of the gastrointestinal tract and reproductive system [*Luk D, Baylin S, 1983; Garewal H et al., 1988; Verma A, 1990; Fernandez C et al., 1995; Jeon J et al., 2003; Bassiri H et al., 2015*].

Thera is a considerable amount of information about the role of aliphatic polyamines in the induction of papilloma in numerous internal organs and tissues. A number of papillomas are determined to be of viral origin. The aspects associated with subtle enzymatic mechanisms which ensure the inclusion of polyamines in normal and hyperplastic cells and the interaction of the same enzymatic processes with the human papilloma virus 18 types (HPV 18) are discussed in a highly informative study of a number of authors [*Jeon J et al., 2003*]. The studies have been conducted in vitro and in vivo. The target of enzymatic research was to the study of transglutaminase 2 (T Gas 2) i.e. one of enzyme families which "catalyzes protein modification by means of polyamine introduction into substrates and the formation of protein crosslinks". Transaminase 2 has been found to interact with oncoprotein E7 of HPV 18. At the same time, according to the authors, the capability of this enzyme to inactivate another HPV16E7 type of human papillomavirus indicates the high prevalence of HPV16 in cervical cancer.

There are also some researches of a considerable interest, aimed to study aliphatic polyamines as risk factors in inducing cervical cancer associated with sexual behavior. Thus, Fletcher S. and co-authors (1991) studied the effect of aliphatic polyamines, identified in seminal fluid, upon the cell cycle as well as ploidy of cervical cells and "primary" epithelial cells, cultured from cervical biopsy samples. The cell growth processes were not impaired, however, in a number of samples, signs of hypodiploidy or hyperdiploidy were observed, depending on the concentration of spermine and spermidine in the seminal fluid. The authors believe that there is an interaction between polyamines of seminal fluid and the DNA of uterine mucous cells, which leads to the ploidy changes, which is often fraught with the development of dysplasia. Clinicians and first of all oncologists and sexopathologists should pay special attention to the fact that the pathogenesis of cervical cancer is conditioned not only by the persistence of the human papilloma virus in situ. It is a known fact that seminal fluid is relatively rich in putrescine, spermidine and spermine. A number of authors [*Fernandez C et al., 1995*] attempted to identify the role of seminal fluid polyamines as cofactors in the development of cervical cancer. The researches of many authors are based on the well-known fact, that aliphatic polyamines (putrescine, spermidine and spermine) undergo oxidation by polyamine oxidase and diamine oxidase, with the formation of oxygen radicals, hydrogen peroxide and reactive aldehydes, which apparently can cause cytotoxic, mutagenic and immunosuppressive in situ effects on the cervical mucosa. According to the results, the authors came to a quite reasonable conclusion that high levels of polyamine oxidase and diamine oxidase in the cervical mucosa should be considered as increased risk factor for cervical cancer, especially in cases with high concentrations of putrescine spermidine and spermine detected in the seminal fluid. At the same time, some authors are quite right to assume that "papilloma-virus infection might synergize the effects of polyamine oxidation, suppressing apoptosis in uterine mucosa cells, carrying potentially oncogenic mutations, which leads to the survival and proliferation of transformed cervical cells", in other words, resulting in their malignancy.

Some aspects concerning the role of aliphatic

polyamines in the origin of papilloma are also presented in the studies [*Koza R et al., 1991*]. Under the conditions of experiment, the authors induced epidermal papilloma in mice DM-1 by a single dimethylbenzanthracene application. It was found, that simultaneously with an increase in the activity of ornithine decarboxylase, the levels of putrescine and spermidine in the same neoplastic tissue sharply increase in papilloma (compared with the control indicators). As the authors note, despite the fact that the epidermis normally contains a large amount of ornithine, the level of the latter in the reborn epidermis with papilloma, exceeds the original by 70 times. According to the authors, under the conditions of the papilloma development, control over local processes ensuring the biosynthesis of specific polyamines is lost, as a result of which the processes of proliferation and differentiation of epithelial tissue are impaired. Some authors determined the polyamine content and ornithine decarboxylase activity in the colon mucosa with adenomatous polyps and without in situ hyperplastic process development [*McCarrity T et al., 1990*]. In biopsy specimens, obtained by colonoscopy with the presence of adenomatous polyps in the mucosa, the content of putrescine increased markedly and at the same time high ornithine decarboxylase activity was determined (compared to the control group). Approximately the same indicators were determined in the rectum mucosa in both groups. The authors believe that in situ detection of aliphatic polyamine (putrescine, spermidine and spermine) levels and ornithine decarboxylase activity i.e. in biopsy specimens of the mucous membrane of the rectum should be considered as informative criteria to determine the course of adenomatous polyps of the mucous colon and their malignancy risk degree. A number of researchers [*Mitchell M et al., 1997*] determined the levels of polyamines and ornithine decarboxylase activity in the cervix with its specific areas as a choice for biopsy: in the mucosa, subject to intraepithelial neoplasia and adjacent regions where epithelial cell structure was relatively preserved, i.e. did not morphologically differ from that characteristic of normal mucosa. It was found that indicators of the polyamine levels - putrescine, spermidine and spermine and the activity of ornithine decarboxylase in the regions of epithelial neoplasia were much higher than in adjacent areas, in which epithelial cell structure was preserved. Kim Y.T. and co-authors (2005) presented some data on diagnostic significance of polyamines, particularly in predicting the risk of metastases to the lymph nodes in squamous cell carcinoma of the cervix. There are informative data on the role of aliphatic polyamines and ornithine decarboxylase in the induction of benign and malignant tumors of the pancreas [*Dunzendrofer U, Russel D, 1978; Feuer E et al., 1999; Simoneau A et al., 2001*]. In pancreatic cancer the level of aliphatic polyamines – putrescine, spermidine and spermine in the pancreas is undoubtedly very high. Moreover, it is known that ornithine decarboxylase is overexpressed in prostate tissue [*Simoneau A et al., 2001*]. It is noteworthy that even in benign prostate diseases, the aliphatic polyamine content and the activity of ornithine decarboxylase are much higher than in benign tumors localized in other organs [*Dunzendrofer U, Russel D, 1978; Derens B et al., 2000*].

Highly informative data on the shifts in the polyamine system, considered as objective criteria for the diagnosis and prognosis of a number of malignant tumors are presented in the researches many authors [*Lipton A et al., 1975; Rudman D et al., 1979; Garnica A et al., 1982; Osswald H et al., 1986; Saydjari R et al., 1989; Lawton F et al., 1990*].

A number of authors [*Lawton F et al., 1990*] examined 39 patients with ovarian cancer to determine polyamine in the urine. Of the total number of patients, 20 patients were resistant to chemotherapy. In resistant patients, high rates of putrescine and spermine fractions were revealed in the urine. In other cases, when the therapy was effective, high spermidine levels were simultaneously determined in the urine in addition to high levels of putrescine and spermine. Researches by Liu R. and other authors (2012) prove the important role putrescine might play in paraclinical diagnostics of malignant neoplasms. In the plasma of healthy volunteers and patients with a number of malignant tumors, the content of diaminopropane, putrescine, spermidine and spermine was determined by high-performance column chromatography. As the study results showed, rather high indices of the above-named polyamines were determined in the plasma of patients with malignant neoplasms as compared to the values recorded in the plasma of healthy volunteers. The authors

came to the conclusion that observed spectrum of polyamines should be considered as diagnostic criteria in the clinical trials for malignant tumors. Uehara N. and others (1980) came to the similar output in determining erythrocyte levels of spermidine and spermine in patients with malignant tumors, considering the levels of these polyamines as markers of the activity of the pathological process. Horn Y. (1982) investigated 190 patients with various malignant tumors over a relatively long time, with strict adherence to the conditions of the relevant protocols. Taking into account the active and inactive phase of the cancer course, the levels of putrescine, spermidine and spermine in the urine of the patients were determined. The authors concluded that the serial determination of polyamine levels in the urine might have its clinical application for monitoring a number of oncological diseases.

While studying metastatic tumors of the gastrointestinal tract, different levels of specific polyamines (putrescine, spermidine and spermine) were found in the urine of patients, depending on the nature and location of tumors in the abdominal cavity and pelvic area [*Lipton A et al., 1975*]. As noted by the authors, spermidine and spermine indices determined in rather high concentrations among the patients observed, turned out to be more informative. A noteworthy fact is that shifts in the polyamine content in the urine of the patients suffering from various forms of lymphomas can serve as additional diagnostic criteria in "Hodgkin's" vs. "non-Hodgkin's" lymphomas [*Thyss A et al., 1982*]. Thus, in Hodgkin's disease, certain patterns of specific polyamine shift in urine were not be detected. Meanwhile, these consistent patterns were revealed in other forms of lymphomas, which made it possible to assess the significance of the polyamine shifts as the chemotherapy positive effect estimate. Researches carried out by Uehara N. and others (1980) also deserve some attention. In various oncological diseases Uehara N. et al. determined the polyamine levels not in urine and plasma, but in erythrocytes. The authors assume that relatively high levels of spermidine and spermine in erythrocytes in patients with malignant tumors (as compared with erythrocytes in the blood of healthy volunteers) might be clinical markers of the pathological process severity. The important role of specific representatives of the polyamine system in the induction of the tumor process was pointed out in the experimental studies, carried out by a group of authors [*Russel D et al., 1974*]. The most informative and fundamental research in terms of studying the role of polyamines in a wide range of oncological diseases was the one carried out by a group of authors [*Russel D et al., 1974; 1975; Russel D, 1977*]. In all the above studies, the key idea that stands out is that levels of polyamine excretion in urine are considered to be cancer monitoring criterion on the one hand, and an early cancer detection test on the other hand. Based on the fundamental researches in this field, the authors propose a hypothesis that polyamines should be observed as clinical indicators to monitor the treatment of malignant tumors, herewith, spermidine only can be considered a "marker of tumor cell death" while putrescine appears to reflect the "proliferative behavior" or "growth fraction" of a tumor [*Russel D et al., 1975*]. There is also a diametrically opposite opinion regarding the changes in the content of polyamines in the cerebrospinal fluid and serum, observed as diagnostic criteria for neoplastic growth in brain structures. Fulton D.S. and co-authors (1982) studied the polyamine content shifts in the cerebrospinal fluid of patients with malignant tumors and in a number of neurological diseases, in which there were no signs of neoplastic growth in the hypophysis. In a comparative analysis of cerebrospinal fluid samples, significant changes in the content of putrescine and spermidine were not found. Approximately the same indicators of polyamines under study were determined in all the groups observed. The authors conclude that shifts in the content of the studied polyamines cannot be considered as diagnostic criteria for the development and course of neoplastic processes in the hypophysis.

The search for effective agents that suppress polyamine synthesis in a number of oncological diseases was aimed at inhibiting specific enzymes, directly involved in the general cascade of reactions in charge of the step-wise synthesis of specific polyamines - ornithine decarboxylase, adenosylmethionine decarboxylase [*Stanek I et al., 1992; Seiler N, 2003*].

Ornithine decarboxylase in mammals acts as the only "launcher" enzyme for the formation of putrescine from ornithine, as indicated previously.

That is why the researches in practical oncology, aimed to find new effective means of inhibiting the activity of ornithine decarboxylase [*Metcalf B et al., 1978*] appeared to be the most productive. According to Meyskens F.L. (1999) the most effective blocker of this class of drugs is the "irreversible" ornithine decarboxylase inhibitor i.e. α-difluoromethyl-ornithine (DFMO).

Wallace H.M. (2009) notes that the twenty-year experience in DFMO testing was a precondition for searching and developing polyamine analogues in oncology that should compete with endogenous polyamines (putrescine, spermidine and spermine) by inhibiting the activity and biosynthesis of ornithine decarboxylase. The studies of Boiko I. V. and co-authors (1998) on the therapeutic efficacy of DFMO in the "treatment" of cervical intraepithelial neoplasia are, in our opinion, of considerable interest. Boiko I. V. studied the effect of DFMO on the expression of epidermal growth factor, which is known to be a marker of cervical intraepithelial neoplasia progression. As shown in the research results, the localization of epidermal growth factor is limited to the basal layer of the epidermis in the normal (control) epithelium, whereas in case of cervical intraepithelial neoplasia, the expression of epidermal growth factor was more common and spread to other, more superficial layers of the epidermis. The DFMO application for therapeutic purposes in cervical intraepithelial neoplasia limited significantly the distribution of epithelial receptors to the epidermal growth factor. This allowed the authors to conclude that the progression of cervical neoplasia is associated with spatial dysregulation of the epidermal growth factor, which can be reversed by using DFMO. The considerable therapeutic efficacy of DFMO was revealed in the researches of a number of authors [*Mitchell M et al.,1998*] in complex therapy of the patients with grade III cervical intraepithelial neoplasia. The use of DFMO was accompanied by a decrease in spermidine/spermine tissue index and an increase in the level of ornithine in the plasma of the patients with cervical neoplasia. According to the authors, the use of DFMO for therapeutic purposes in various increasing doses did not cause toxic disorders in patients with III severity degree of cervical neoplasia. The efficacy of DFMO application was also revealed in the complex treatment of multiple adenomas, which prevented significantly the risk of colorectal neoplasia [*Laukaitis C et al., 2011*]. Based on previously conducted experimental and clinical studies (including their own research), the scientific elaboration of Bassiri H. and co-authors (2015) on the use of specific doses of DFMO in the neuroblastoma complex therapy in children deserves great attention. The noteworthy fact is that the symptomatic and pathogenetic therapies of a number of oncological diseases are carried out due to the increasing use of endogenously active substances or their synthetic analogues, since it is the endogenous biological factors that, under the conditions of impaired in situ metabolism, largely determine the nature and features of many oncological diseases.

The embryonic proteoglycan EPOM developed by a leading scientist, Honored worker of science of Armenia, a foreign member of the Russian Academy of Sciences, professor Mkrtchyan L.N. is nowadays widely applied in practical oncology as an effective prophylactic factor in a number of oncological diseases. There is also another approach in which a "low polyamine diet" is recommended for cancer patients. In his review article Wallace H.M. (2009) notes some positive results achieved by Moulinoux group in Rennes by using a similar diet in hormone resistant prostate cancer [*Cipolla B et al., 2003; 2007*]. This approach is believed to be highly promising in oncology, since currently the "low polyamine diet" has not found its proper use as an "auxiliary symptomatic therapy" in the treatment of malignant neoplasms. The assumption we have put forward is highly valid, since the levels of polyamines in numerous food and alcohol products vary within rather wide limits.

Along with numerous social factors, adherence to the correct diet, balanced in nutrients containing proteins, fats and carbohydrates is one the factors that contribute to the high quality of life. The combination of natural food products with various preservatives, flavor compounds, natural ingredients being replaced with the artificial ones, as well as the introduction of food additives have an unfavorable effect on human health.

The polyamine (primarily putrescine) content in food products most commonly used by people in many countries around the world has not been the subject of a special study so far. Consequently, we

consider it appropriate to introduce a table of putrescine content in some food products (Table) based on generalized results found by researchers from different countries, which are summarized in a highly informative report [*Ali M et al., 2011*].

As seen in the table, the content of putrescine in various food products is far from being equivalent. Among vegetables and greens, thus relatively high indices of putrescine were recorded in sauerkraut, fried potatoes, green pepper; among fruits - in oranges, tangerines, lemon, and also in orange juice. In other fruits such as cherries, bananas, kiwi and apples, much lower (almost minimal) indicators of putrescine were found. Very low rates of putrescine were detected by means of liquid chromatography in meat products, such as ground beef, beef liver, salami, bacon as well as in a number of domestic animals, chicken, duck and turkey. While speaking about fish products, high content of putrescine was found in raw cod and the highest level of putrescine among amphibians was found in crab. Red and white wines have relatively low levels of putrescine content.

Polyamine system studies, from the point of food safety, should be carried out among all the age groups, taking into account peculiarities of nutrient intake among rural and urban population.

The suggested scientific and methodological approach seems to be quite reasonable, since the "harmful" effect of a frequent (if not to say everyday) use of large quantities of food products containing high concentrations of putrescine hasn't been yet determined.

The fact that relatively high concentrations of putrescine stimulate hyperplastic processes exclusively in all organs and tissues of mammals (including humans) has been found by fundamental and applied research over the last 15-20 years. In this regard, it is necessary to note an important point, that tumor cells have the ability to "absorb" polyamines, contained in the nutritional products, as well as polyamines produced in bacteria persisting in the gastrointestinal tract of higher mammals [*Kalac P, Krausova P, 2005; Ali M et al., 2011*]. Moreover, there is certain information on the links between the high level of polyamines (especially putrescine) and the risk of malignant diseases [*Catros-Quemener V et al., 2003*]. Taking into account the fact that high putrescine levels in mam-

Table

The putrescine content in various food products (*mg/kg or mg/l*)

Product name	Put	Researchers (publication authors)
Vegetables		
Fermented cabbage	146.0	Kalas P. et al., 1999
Green pepper	54.7	Nishibori N. et al., 2006
Ketchup	52.5	Kalac P. et al., 2002
Crispy fried potatoes	40.2	Bardocz S. et al., 1995
Leek	24.5	Nishimura K. et al., 2006
Potato (cooked)	21.6	Bardocz S. et al., 1993
Celery	17.1	Nishibori N. et al., 2006
Garlic	13.1	Cipolla B.G. et al., 2007
Spinach	12.9	Kalac P. et al., 2002
Tomatoes	10.6	Okamoto A. et al., 1997
Potato (fresh)	9.7	Bardocz S. et al., 1993
Red pepper	2.3	Cipolla B.G. et al., 2007
Fruits. Fruit juice		
Orange	137.0	Eliassen K.A. et al., 2002
Tangerine	122.0	Eliassen K.A. et al., 2002
Orange juice	85.0	Eliassen K.A. et al., 2002
Lemon	41.0	Nishimura K.et al., 2006
Banana	15.3	Lavizzari T. et al., 2006
Raisins	10.0	Cipola B.G. et al., 2007
Apple juice	5.1	Saaid M. et al., 2009
Cherry	1.6	Nishibori N. et al., 2006
Kiwi	1.2	Cipolla B.G. et al., 2007
Apple	1.0	Bardocz S. et al., 1993
Meat products		
Ground beef	8.9	Bardocz S. et al., 1993
Chicken, duck, turkey	2.9	Bardocz S. et al., 1993
Beef liver	1.0	Nishimura K. et al., 2006
Salami	0.5	Cipolla B.G. et al., 2007
Beckon	0.3	Cipolla B.G. et al., 2007
Seafood		
Crab	122.0	Eliassen K.A. et al., 2002
Cod (raw)	28.0	Bardocz S. et al., 1993
Crayfish	0.1	Cipollo B. G. et al., 2007
Tuna (fresh and canned)	No	Veciana-Nogues M.T. et al., 1997
Milk products		
Eggs (chicken)	0.3	Bardocz S. et al., 1995
Milk (cow)	0.1	Bardocz S. et al., 1993
Mayonnaise	0.1	Cipolla B. G. et al., 2007
Butter	No	Cipollo B. G. et al., 2007
Wine		
Red wine	5.1	Nishimura K. et al., 2006
White wine	3.5	Nishimura K. et al., 2006

mals should be considered a risk factor for the induction of many oncological diseases, the research on the definition of putrescine in foods that are periodically and strategically consumed by urban and rural populations is, in our opinion, extremely promising.

As a part of the problem discussed in this chapter, oncologists have a broad prospect in terms of an extraordinary, but quite reasonable, in our opinion, treatment tactics i.e. subsidiary means of "symptomatic therapy" of malignant diseases, based on the diets with the lowest possible polyamine content.

α -Synuclein is the one among the synuclein family which is most frequently expressed in tumor cells in a wide range of oncological diseases. α -Synuclein, also referred to as "breast carcinoma specific gene I-BCSGI" was originally cloned by filtering breast cancer cells. Subsequent studies showed that α-synuclein is not equally expressed in different types of cancer, especially at the late stages. It was herewith rarely expressed in healthy tissues of the perifocal regions (non-neoplastic adjacent tissues). Patients with α-synuclein-protein-positive breast cancer are characterized by lower survival rate as compared with patients without signs of α-synuclein expression. In addition, recent studies have shown that over-expression of α-synuclein can stimulate proliferation, invasion and metastases of malignant cells in breast cancer.

α-Synuclein can also disrupt the normal mitotic division, leading to multinucleation and faster growth of breast cancer cells. α- and β-Synucleins are also expressed in some types of cancer: in 75% cases of astrocytoma, in 38% cases of oligodendroglioma and 76% cases of medulloblastoma. It was found that at least one type of synuclein is expressed in 80% of cases in ovarian cancer meanwhile the expression of all three types of synucleins was simultaneously observed in 42% of cases.

Colorectal cancer is the third most common malignant neoplasm and the third leading cause of cancer death worldwide. Conventional methods of treatment by means of surgical invasion and adjuvant therapy obviously result in the improvement in the patient's condition and survival increase. However, about 50% of patients die within 5 years because of metastases or the disease relapse. In addition, tumor invasion and metastases to regional lymph nodes are important factors in the colorectal cancer prognosis determination [*Fernandez C et al., 2004*].

α- and β-Synuclein expression in colorectal cancer has not been systematically studied. However, recent researches suggest that α- and β-synucleins are expressed in colorectal cancer as well, that also allows to consider them to be biomarkers for the disease severity assessment.

To sum up the above-mentioned literature data, one might be come to the following conclusion.

Firstly, the study of aliphatic polyamines (putrescine, spermidine and spermine) and α-synuclein in erythrocytes and plasma is a very promising tendency in modern oncology, since it is aimed at identifying relatively informative criteria for early diagnosis of malignant tumors.

Secondly, indicators of polyamine levels in the erythrocyte and plasma should obviously be considered objective criteria in the assessment of the malignant tumor treatment effectiveness.

Thirdly, in high-precision studies such as high-performance liquid chromatography, aliphatic polyamines (putrescine, spermidine and spermine) must be obligatorily observed in complex, since each of the above-named polyamines must be given a specific role, both in early diagnosis and prognosis of malignant tumors.

Fourthly, a special attention should be given to the shifts in spermidine content, since the latter can be considered as an objective marker i.e. "killer factor" in cancer cell destruction.

The role of polyamines and gamma synuclein in Helicobacter Pylori infection in the gastric cancer pathogenesis is the subject of extensive study in modern oncology and gastroenterology.

Approximately half of the world's population is infected with H. pylori, and most colonized people develop coexisting chronic inflammation [*Peek R, Blaser, 2002*].

The relationship between H. pylori and gastric cancer has been a subject of controversy for years. However, several studies have now provided clear evidence that H. pylori infection significantly increases the risk of stomach cancer [*Uemura N. et al., 2001*].

Among infected people, peptic ulcer develops in approximately 10%, gastric adenocarcinoma in 1-3%, and lymphoma associated with mucosa-as-

sociated lymphoid tissue in 0.1% [*The EUROGAST Study Group, 1993; Stolte M, 2002; Peek R, 2006*].

Eradication of H. pylori significantly reduces the risk of gastric cancer in infected people without precancerous lesions [*Wroblewski L et al., 2010*].

The effect of H. pylori products on macrophages leads to increased regulation of the arginase II enzyme [*Gobert A et al., 2002*]. Helicobacter pylori induces macrophage apoptosis by activation of arginase II and the induction of ornithine decarboxylase, which leads to an increase in the level of polyamines [*Chaturvedi R et al., 2004*]. Induction of polyamine oxidase 1 by Helicobacter pylori causes macrophage apoptosis by hydrogen peroxide release and mitochondrial membrane depolarization [*Cheng Y et al., 2005*]. Helicobacter pylori-induced macrophage apoptosis requires activation of ornithine decarboxylase by c-Myc [*Gobert A et al., 2002; Wroblewski L et al., 2010*].

Some studies have found out a strong correlation between the expression of SNCG in primary tumors and distant metastases in many types of cancer, including cancer of the esophagus, stomach and large intestine [*Lipton A et al., 1975*].

Neuronal protein synuclein-gamma (SNCG) expression was found out to increase in gastric cancer, especially in metastatic tissues [*Wang Y, 2014*]. After analyzing the relationship between the expression of SNCG and the clinical and pathological factors of patients with gastric cancer, a significant relationship was found between the SNGG expression, the depth of tumor invasion and the stage of cancer [*Yanagawa N et al., 2004*]. Demethylation of the synuclein gamma gene CpG island in primary gastric cancers and gastric cancer cell lines [*Surgucheva I et al., 2013*]. Cell-specific post-transcriptional regulation of gamma-synuclein gene by micro-RNAs [*Gupta A et al., 2003*]. Hypomethylation of the synuclein gamma gene CpG island promotes its aberrant expression in breast carcinoma and ovarian carcinoma [*Czekierdowski A et al., 2006*]. The role of CpG islands hypomethylation and abnormal expression of SNCG in ovarian cancer [*Wang, Y et al., 2014*]. Hypoxia-Inducible lncRNA-AK058003 promotes gastric cancer metastasis by targeting γ-synuclein.

In this aspect, previous studies should be the subject of substantial revision, according to which in case of prolonged persistence of Helicobacter Pylori in the stomach, an enhanced synthesis of polyamines and cumulation in situ of oligo- and aggregated gamma synucleins occurs in mucous membrane cells. It is possible that all of the abovementioned factors in total directly and/or indirectly have a stimulating effect on the processes of the malignancy of gastric mucosal cells.

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