

Urinary cytological screening with follow-up

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Abstract

This retrospective study aims to offer an analysis of urinary cytology performed on records of the Cytodiagnosis Service of Modena Policlinics Surgical Pathology Department on 2769 exams, corresponding to 892 patients relative to the year 2004 with follow-ups to June 2006. The epidemiological profile of the patients is described, the incidence of diseases discussed, and the cyto-histological correlation with samples taken from patients who underwent surgery. Patients are mainly above 65 years of age and predominantly males, 23% developed bladder cancer, of which 27% recurred. The more frequent morphologic categories have been “*Hyperplastic cells*” and “*Inflammation*”, “*Negative for neoplastic cells*” with 39.7%, 24.4% and 13.8% respectively. The cyto-histological correlation has been possible only in 50% of the positive cases, mainly because of lackness of corresponding biopsy: in this former cases the concordance was 92%. In the last concluding chapter the role of syntropy in the prevention of bladder cancer will be discussed.

Introduction

Purposes of urine cytological exams are different and various and they range from diagnostic, to prevention, screening and follow-up.² Cytological exams can lead to early diagnosis of bladder cancer, without any major invasive technique. It is a mini-invasive therapy (endoscopy ablation) with low costs and a convenient costs/benefits ratio which makes it non-negligible anymore today. In preventive medicine this type of exam reduces considerably the incidence and mortality of bladder cancer, as it also happens for pap-tests, where the mortality rate is today inferior to 1%. Finally, the cytological follow-up allows to safely accurately evaluate the patient outcome, saving money and resources of the National Health Service.

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² Blanz B., Jochims E. et al. (2003), *The role of urinary cytology for detection of bladder cancer*, Science Direct, June 2003: 304-308.

Cytological Pictures

- Inflammation

Inflammation implies the presence of neutrophils and typical inflammation disorders, such as cytolysis that point to the increase of the nucleus size, without chromatin or nuclear membrane, which appears irregular and of tint affinity.³

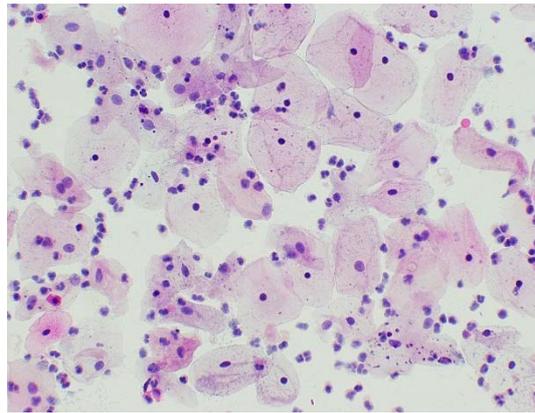


Figure 1: case number 153/04 (20x), G.A, ♀ i 45 years, first diagnosis - Flogistic finding

- Dystrophy

Dystrophy is here intended as cellular size alterations. This physiological condition in adult age is generally associated to inflammatory lesions. Cells appear shrunken, with diminished size and sometimes distorted, not regular anymore, cylindrical, and at times gathered in small groups.⁴

- Infective lesions

In cytological slides micro-organisms may be found, often as the result of pollution. In the following figure colonies of organisms are seen over a landscape otherwise normal. Also bacteria, fungi and parasites can be found. Microbiological exams are necessary in order to assess this situation.

³ Koss L.G., *Diagnostic Cytology*, Lippincott Company, IV Edizione 1992;

⁴ DeMay R.M., *The art and science of cytopathology*, ASCP Press, III Edition, 1998;

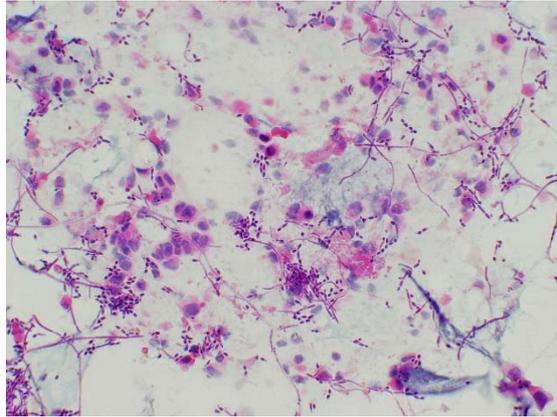


Figure 2: case 4016/04 (20x), G.P, male, 81 years - Presence of dysplastic cells with fungi (*Alternaria*)

- Hyperplasia

Hyperplasia consists of a number of elements belonging to a specific tissue which may present a modest nucleus increase with cytoplasmic reduction.⁵

- Neoplastic lesions

Neoplastic picture remember typical cytological alterations, like nucleus size increased with chromatin alterations, increase in the number of nucleolus that lead to dismetic and polymorphic cells.⁶

- Ancillary Techniques in diagnosing

Cytological exams are wonderful for their diagnostic efficiency, but in some circumstances, for instance when dealing with low grade carcinoma, they must be associated with other techniques and with a clinical-laboratory assessment. In these situations the cytological exam alone may reveal false negative. This happens when the ancillary technique in diagnosis is required, such as cytometry, microsatellite analysis, bladder tumor antigen test, BCLA-4 and NMP immunocyt.⁷

⁵ Enciclopedia Italiana, vol X, Istituto dell'Enciclopedia Italiana, I edizione, 1949.

⁶ Takahashi M., *Citologia del cancro*, Verducci Editore, III Edizione, 2000.

⁷ Takeuchi Y, Sawada Y, Yabuki D, Masuda E, Satou D, Kuroda K, Tajima M, Sawamura Y, *Clinical study of urine NMP-22 as a tumor marker*, *Aktuel Urol* 2003 Jul; 34:265-72.

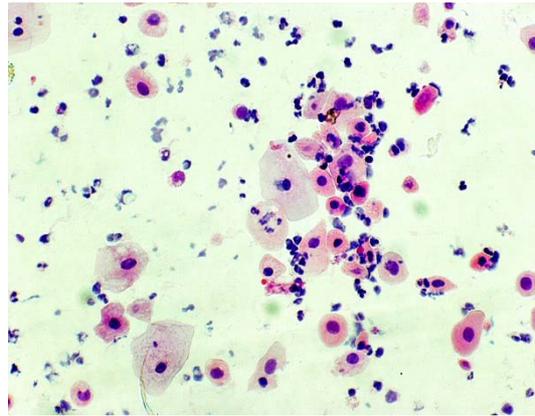


Figure 3: case 3358/04 (20x), D.G ♂, 46 years, first diagnosis, presence of hyperplastic cells

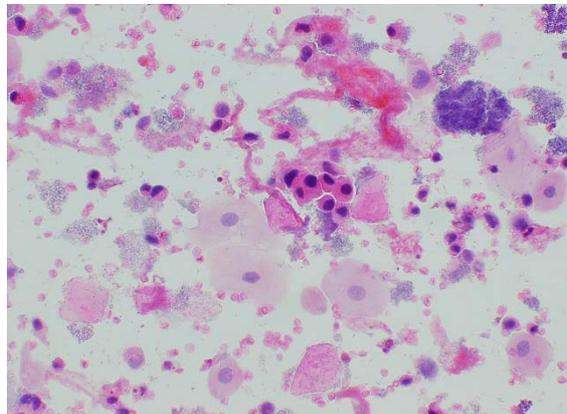


Figure 4: case 1727/04 (20x) Dysplastic cells, P. N ♂ 83 years

AIMS of the study

This retrospective study is based on a sample of urinary cytology collected at the surgical pathology division of the Modena policlinic in 2004 with follow-up to June 2006.

The aims are:

- assess an epidemiological profile for sex and age in relation to different diagnostic settings;
- identify the incidences of cytological pictures;
- search for a fil rouge that may explain the progression from a diagnosis to another (inflammation - cancer);
- verify cyto-histological correlations;
- consider the value of endoscopic therapy for positive cases underlining the importance of urinary cytological screening as prevention instrument.

Materials and Methods

Data was collected from the database of the archive division. Statistical analysis was performed using morphologic code (SNOMED). The follow-up did not take into account those patients that had a first diagnosis in the follow-up period. All the cytological exams of the year 2004 were considered, for a total of 2769 exams relative to 892 patients. The follow-up was performed from 6 months up to 30 months. In 2004 a total of 201 patients were confirmed positive for bladder cancer using biopsy. SNOMED considered:

- negative for atypical cells
- dystrophy
- blood
- inflammation
- necrosis
- inadequacy
- bacteria
- parasite
- fungi
- morphologic description
- cytological alterations NOS
- hyperplastic cells
- mild dysplasia

- moderate dysplasia
- severe dysplasia
- dysplasia
- atypical cells, probably malignant
- malignant cells
- CIS
- invasive Transitional carcinoma

Results

All the patients with a cytological exam in 2004 were considered. A total of 892 patients and 2769 cytological exams. The study includes 201 patients who were follow-ups in 2004. Some of these patients had their first exam in 1991, when the database was started. Among the 892 patients, 290 were female and 602 male. Cytological exams were performed up to 4 times in the same year for the same patient.

Age			Mean age	
	Males	Females	Males	Females
up to 20	0	1	0	18
21-30	6	3	27	27
31-40	16	16	36	36
41-50	49	30	46	46
51-60	101	41	56	56
61-70	168	70	66	66
71-80	180	77	76	76
81-90	68	41	86	85
91 and over	14	11	96	96
Total	602	290	61	56

Table 1: sex and age distribution of the sample cases

The first consideration is that the male population is twice the female population and that patients are mainly in the age group 61 to 80.

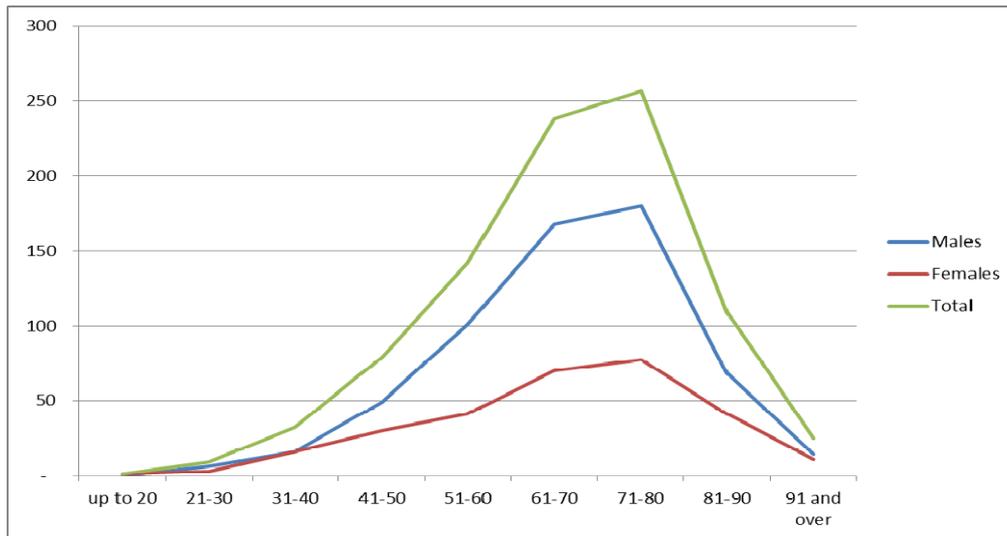


Figure 5: sex and age distribution of the sample cases

The following table shows that the more frequent categories are dystrophy (39.69%), hyperplasia (24.44%) and inflammation (13.79%).

SNOMED	M	%	F	%	MF	%
009450 Negative for atypical cells	12	1.99	29	10.00	41	4.60
056000 Dystrophy	239	39.70	115	39.66	354	39.69
037000 Haemmorrhage	6	1.00	0	-	6	0.67
069780 Inflammation	59	9.80	64	22.07	123	13.79
036330 Fluid-emativ finding	1	0.17	0	-	1	0.11
009010 Inadequacy	4	0.66	1	0.34	5	0.56
E04000 Miceti	0	-	1	0.34	1	0.11
009350 Morphologic description	16	2.66	5	1.72	21	2.35
072000 Hyperplasia	171	28.41	47	16.21	218	24.44
069000 Cytological alteration NOS	4	0.66	1	0.34	5	0.56
074006 Mild dysplasia	34	5.65	13	4.48	47	5.27
074000 Dysplasia	50	8.31	13	4.48	63	7.06
074008 Strong dysplasia	1	0.17	0	-	1	0.11
069760 Atypical cells probably neoplastic	2	0.33	1	0.34	3	0.34
800130 Malignant cells	3	0.50	0	-	3	0.34
TOTAL	602	100%	290	100%	892	100%

Table 2: Morphologic code distribution by sex

Comparisons among males and females are done using the column percentages. Among females stronger incidence is found in “*inflammation*” (22.07%) and “*negative for atypical cells*” (10.00%), whereas among males a higher proportion of “*hyperplasia*” (28.41%) is observed.

The following table shows the morphologic distribution by age and sex.

SNOMED	Age mean value		
	Males	Females	Total
009450 Neg. For atypical cells	68	65	67
056000 Dystrophy	67	66	67
037000 Haemorrhage	71	-	71
069780 Inflammation	68	68	68
009010 Inadequacy	62	55	57
009350 Morphologic description	69	64	67
072000 Hyperplasia	67	64	66
069000 Cytological alteration NOS	70	70	70
074006 Mild dysplasia	70	70	70
074000 Dysplasia	70	67	69
069760 Atyp cells probably neoplastic	71	69	70
800130 Malignant cells	71	-	71
Total	69	66	68

Table 3: Morphologic code distribution by sex and mean age values

This distribution results to be uniform.

Positive cytological exams comprehend: “*cytological alteration NOS*”, “*mild dysplasia*”, “*dysplasia, severe dysplasia*”, “*atypical cells probably malignant*” and “*malignant cells*”.

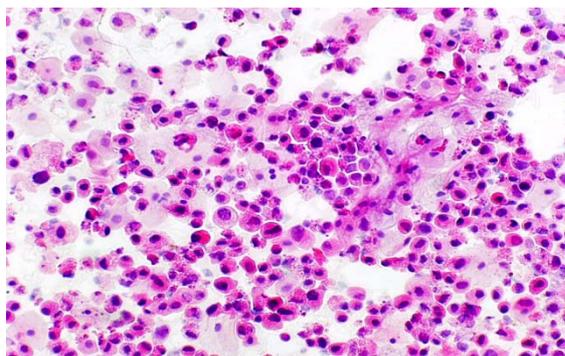
Many categories among which: “*cytological alteration NOS*”, “*presence of dysplastic cells intensely*”, “*presence of atypical cells probably malignant neoplastic and neoplastic cells*” were not followed by biopsies, except a case of “*cytological abnormalities NOS*”, consequently they cannot be cyto-histological correlated. In other two categories, presence of “*mild dysplastic cells*” and presence of “*dysplastic cells*” allowed cyto-histological correlations in 50% of the cases. The positive cytological exams were 24% of which confirmed by biopsy only 8%.

	Biopsy		Percentages	
	Positive	Negative	Positive	Negative
Cytological alteration NOS	1	0	0.52	-
Mild dysplasia	119	10	61.66	58.82
Dysplasia	73	7	37.82	41.18
Severe dysplasia	0	0	-	-
Atypical cells probably malignant	0	0	-	-
Malignant cells	0	0	-	-
Total	193	17	100.00%	100.00%

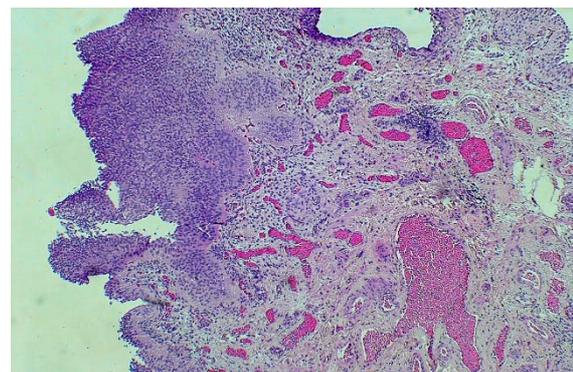
Table 4: morphologic categories with corresponding biopsy results

- Sensibility and specificity

Analysis of case studies reveals 8 false negative: SNOMED cases with negative cytology and positive biopsy. Symmetrically 17 SNOMED cases with positive cytology and negative biopsy were also false positive, pointing to a specificity of 92% and a sensibility of 96%.



case 275/04 (20x), F.G ♂ 80 years, dysplastic cells



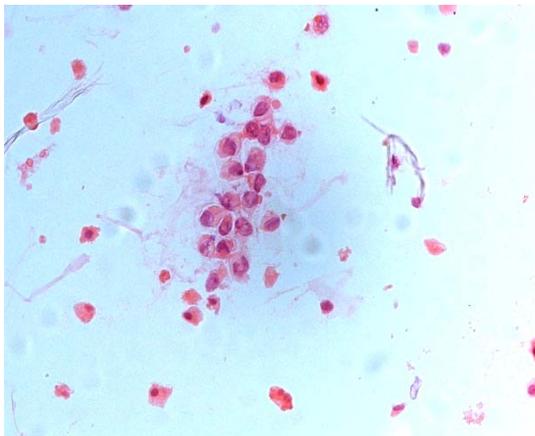
case 993/04 (10x), F.G ♂ 80 years - G2pTa

Discussion

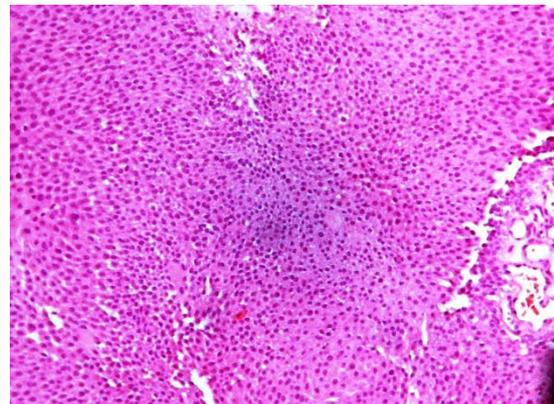
The sample was large (892 patients), with a predominant age between 61 and 80 years, both for males and females. The age distribution divided per gender is uniform and rather homogeneous and tends to a Gaussian distribution which peaks around 70 years of age.⁸ On the contrary for the first and second decade the number of patients is too small and consequently not significant.

Urinary cytology was performed by 86% of the population after 50 years of age, of which 56% were in the range 60-80 years. Only 14% of the cases are relative to young adults. Cytology is required if the patient has symptoms at the emunctory apparatus. These symptoms, such as strangury and dysuria, are typical among men in adulthood, after 60 years of age⁹ and urine testing is often required as a control. It should be stressed that 86% of malignant tumors of the bladder, diagnosed on cytology, comes from the seventh decade, thereby leading to an intensification of the cytological controls and a consequent greater number of cases in this age group. As for cytology at a young age it can be argued that it is related to acute episodes of urinary tract infection, common among young men.

The distribution by categories shows a maximum for dystrophy (39.69%), followed by hyperplasia (24.44%) and inflammation (13.79%) with a stronger incidence of inflammation and negative for atypical cells among female and a higher proportion of hyperplasia among the male population.



case 4616/04 (20x), R.M ♂ 50 years,
dysplastic cells



case 25169/04 (20x), R.M ♂ 50 years,
G1pTa

In findings of atypical cells and inflammatory the majority of patients are female. But compared to all the diagnostic categories women are less present. It is plausible that

⁸ Colton T., *Statistica Medica*, Piccin, IV Edizione 1991.

⁹ Cotran R.S., *Robbins, Le basi patologiche delle malattie*, Piccin Editore, VI Edizione, 2001.

the SNOMED of absolute negativity is more common in females. In inflammatory finding the prevalence of females can be interpreted considering the fact that the episodes of inflammation, especially when acute, are typical of the female world. The 66% of hyperplastic cells is concentrated in the age group 60-80 years. This data coincides with the average age in which cytological examinations are most required, on the other hand, however it should be stressed that the majority of this population is made of follow-ups, especially those over the age of 80. On the contrary the first diagnosis is mainly found among the population with ages ranging from 20 and 50.

Dystrophy is observed as an average 10 years earlier than hyperplasia and together with inflammation shows a close and statistically significant association with patients who have positive cytology for bladder cancer, especially in the follow-up with more than 95% of patients with positive biopsy. The SNOMED "*negative finding atypical cells*" has a relatively uniform distribution by age and represents mainly a diagnosis made on the controls of follow ups. The SNOMED presence of "*mild dysplasia*" represents the first stage towards the onset of cancer and of relapse and is in many cases an initial diagnosis. It also includes patients who remain stationary on mild dysplasia. Non-negligible effects of radiation therapy and chemotherapy, decomposer of the tropism of the bladder and mucosa, which can affect the normal turnover of the epithelial surface of the bladder, and can be associated with an increase of dystrophic, inflammatory and presence of hyperplastic cells, even after endoscopic therapy of surgical ablation of the neoplastic lesions. The morphology code presence of dysplastic cells has fairly uniform distribution in all the age classes, with the largest incidence between 60 and 80 years of age, similarly to the finding for hyperplastic cells. For paradigmatic colon cancer, where the precancerous lesion, the polyp, can change from hyperplastic and neoplastic to dysplastic, the levels of the urothelium and hyperplasia are predisposing factors although not yet proven as precancerous. The SNOMED only morphological description refers generally to young cases, for which details of cytological abnormalities are not present. It may also refer to elderly cases which replaces the code of negativity. Other codes as "*hemorrhagic*", "*cytological alterations NOS*", "*presence of atypical cells probably neoplastic*", "*inappropriate material*", "*presence of malignant neoplastic cells*" and "*fungi*" have a very low incidence, with less than 10 cases each, which corresponds to a percentage lower than 0.5%. It is therefore possible to arrive to the conclusion that the number of cytological inadequate, with the method under consideration (filtration on a polycarbonate membrane), is 0.2%. This finding supports the validity of the test. The majority of cancers detected with cytology are present in the follow-ups (69 %). In 2004 carcinomas reached 15%, whereas in 2005 and 2006 were 10% and 6 % respectively. In 2004 a total of 201 patients were treated with bladder cancer. This value represents 23% of all the 892 patients. Of these 201 cases, 27% relapsed during follow-up. In this series, 10% of malignant neoplasm of the bladder developed before age 50, usually within patients who did not have a previous clinical history of urinary

cytology. Relapses occur mainly (70%) among people with more than 60 years of age. About cyto-histological correlation, some diagnostic categories such as “*cytological abnormalities*”, the presence of “*dysplastic cells intensely*”, the presence of “*atypical cells probably malignant neoplastic and neoplastic cells*” had all the cases with no biopsy. This is important since if cytology is positive biopsy is not performed. In some cases the information about biopsy was not available since these patients had died due to their elder age. As already described the results about the test point to a specificity of 92% and a sensibility of 96% which can increase slightly through a more thorough quality control. More than 90% of malignant tumors are considered in the very early stages of pTa - T1 and the treatment of choice is the endoscopic ablation, whereas in T2-T3 is cystectomy, which is surgically done. Bladder tumors recurrence was 27% whereas healing was at 73%.

Conclusion: Cytological exam and Syntropy

A progression that goes from “*inflammation*”, “*dystrophy*”, “*hyperplasia*”, “*dysplasia*” and “*cancer*” is observed in the field of natural medicine, such as homeopathy¹⁰, but not still accepted by traditional medicine, since it does not recognizes as precancerous a flogistic situation.

Actually both approaches might be right, since it only depends from the point of view. In other words it depends from where we apply causality and this allows me to introduce the concept of syntropy. Let's imagine a 75 years old man with a long history of urinary disorders, but who never had cancer, who is told he has bladder cancer. Was that not predictable? Was that not avoidable? I believe yes. Bladder cancer develops, in the majority of cases, from an inflammation disorder as it is well described in this article. If we have an inflammation disorder this does not necessarily imply that we will have cancer, it only means that something is trying to catch our attention. Why don't we give the appropriate attention to this warning signal? The theory of syntropy suggests that we are constantly in-between a flow of information which comes from the past (perceptions, symptoms and warning signals) and information that comes from the future, mainly in the form of emotions and feelings. The outcome is based on our free-will and determines if we will pay appropriate attention to the warning signals.

Therefore, when we have recurrence in flogistic disorders over a significant period of time (at least a few years) we should start to think that we have an increased risk to develop bladder cancer. At that stage medicine CAN PREVENT IT, correcting our lifestyle habits. But the emotional content which is associated to these disorders and

¹⁰ Grieco A., *Vivere alcalini, vivere felici*, Nuove Esperienze 2013

which “anticipates” a possible future state, might scare us and stop from taking actions which could prevent the degeneration into a cancer.

Introducing the concepts of syntropy in the field of medicine may therefore result in less money spent, less medicines and better health. An important optimization of resources and money. A syntropic approach to health can help us not only to prevent cancer and save a significant number of lives, but can contribute to cost reductions and an efficient prevention approach, which is now becoming always more important and actual for the National Health Services.

Acknowledgments: a particularly thank to professor MC De Gaetani who trained me in cytology whom, and without whom this work would have not been written, and dr. Antonella Vannini and dr. Ulisse Di Corpo, who opened my mind to the new vision of syntropy.

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