Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Case report

Family with a multiple cancer syndrome

[1]Daciana N. Chirilă, [1]Nicolae A. Turdeanu, [1]Nicolae A. Constantea, [2]Radu Popp, [3]Ovidiu Bălăcescu, [1]Tudor R. Pop, [4]Cătălina I. Bungărdean, [5]Constantin Ciuce

[1] Vth Surgical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, România; ; [2] Department of Genetics "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca; [3] Functional Genomics, Proteomics and Experimental Pathology Laboratory, The Oncology Institute „Ion Chiricuţă" Cluj-Napoca; [4] Department of Pathology, Clinic County Hospital, Cluj-Napoca, România; [5] "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Ist Surgical Clinic, Cluj-Napoca, Romania.

Abstract. Objective: We present the clinical data of a family with a multiple cancer syndrome. Material and Methods: we made a chart of this family and analysed the clinical data offered by some members of the family; the genetic tests were not available for the members of the family. Results: The evolution of the cancers was good but not in all the cases. Many of them are alive, and in good condition. Conclusion: the family with these multiple malignant tumors can be incorporated into a Lynch syndrome, but we do not have the genetic tests for the 5 known modified genes in hereditary nonpolyposis colorectal cancer syndrome.

Key Words: multiple cancer syndrome, familial agregation, survival.

Corresponding Author: D.N. Chirilă, dacianachirila@gmail.com

Introduction

Cancer is a major public health problem in many parts of the world. Nowadays, one in 4 deaths in the United States is due to cancer. A total of 1,596,670 new cancer cases and 571,950 deaths from cancer were projected to occur in the United States in 2011 by the American Cancer Society. The published data showed an overall cancer incidence rates stable in men in the most recent time period, after decreasing by 1.9% per year from 2001 to 2005; in women, the incidence rates have been declining by 0.6% annually since 1998 (Siegel *et al* 2011), largely due to decreases (Jemal *et al* 2010) in the 3 major cancer sites in men (lung, prostate, and colorectum) and 2 major cancer sites in women (breast and colorectum).

The estimation for percentage of colorectal cancers belonged to a familial cancer syndrome is between 15-20%. Lynch Syndrome, known also as Hereditary nonpolyposis colorectal cancer (HNPCC), is a syndrome that associates many malignant tumors, transmitted in an autosomal dominant inheritance. The syndrome was described in 1966 by Henry T. Lynch who analysed two separate midwestern American families with a marked predisposition to various cancers, even if the association of different cancers was originally described in 1913, by Warthin, who observed an inherited predisposition to cancers of the colon, stomach, and endometrium (Warthin 1913, cited by Geiersbach and Samowitz 2011). It accounts for 1-10% of the total number of colorectal cancers occurred in population (Marra and Boland 1995; Aaltonen *et al* 1998; Lynch 1999; Ponz de Leon *et al* 1999; Katballe *et al* 2002; Raedle *et al* 2002).

Material and method

We analyse a family in which were diagnosed a lot of primary malignant tumors. It was not performed a genetic test for identifying if there is any of known mismatch repair genes mutated in a Lynch syndrome. We consider that with such association of malignant tumors, according to the Amsterdam criteria, the members of this family may be affected by this familial cancer syndrome.

Results

There were 9 family members diagnosed and treated for malignant tumors (4 men and 5 women) in three successive generations. In the first generation all four children were diagnosed with cancer (two sisters and their brother with large bowel cancers, two sisters with endometrial cancers and one sister with gastric cancer). Totally in the whole family extended, the most common cancer met, was a large bowel one, found in 8 individuals (4 men and 4 women). A proximal location was found in one patient, the others had usually a sigmoid cancer. Another cancer (the second primary) associated with HNPCC tumors was found in two patients, both women: a gastric one developed late in life (at the age of 78 years), after 16 years, and an endometrial one developed 19 years after a colon cancer. Another patient, member of this family, was diagnosed with a benign brain tumor, few years after the large bowel cancer. Also, the patient CN, developed another tumor located on the large bowel, two years after a previous one, located on the sigmoid colon. At that time, the

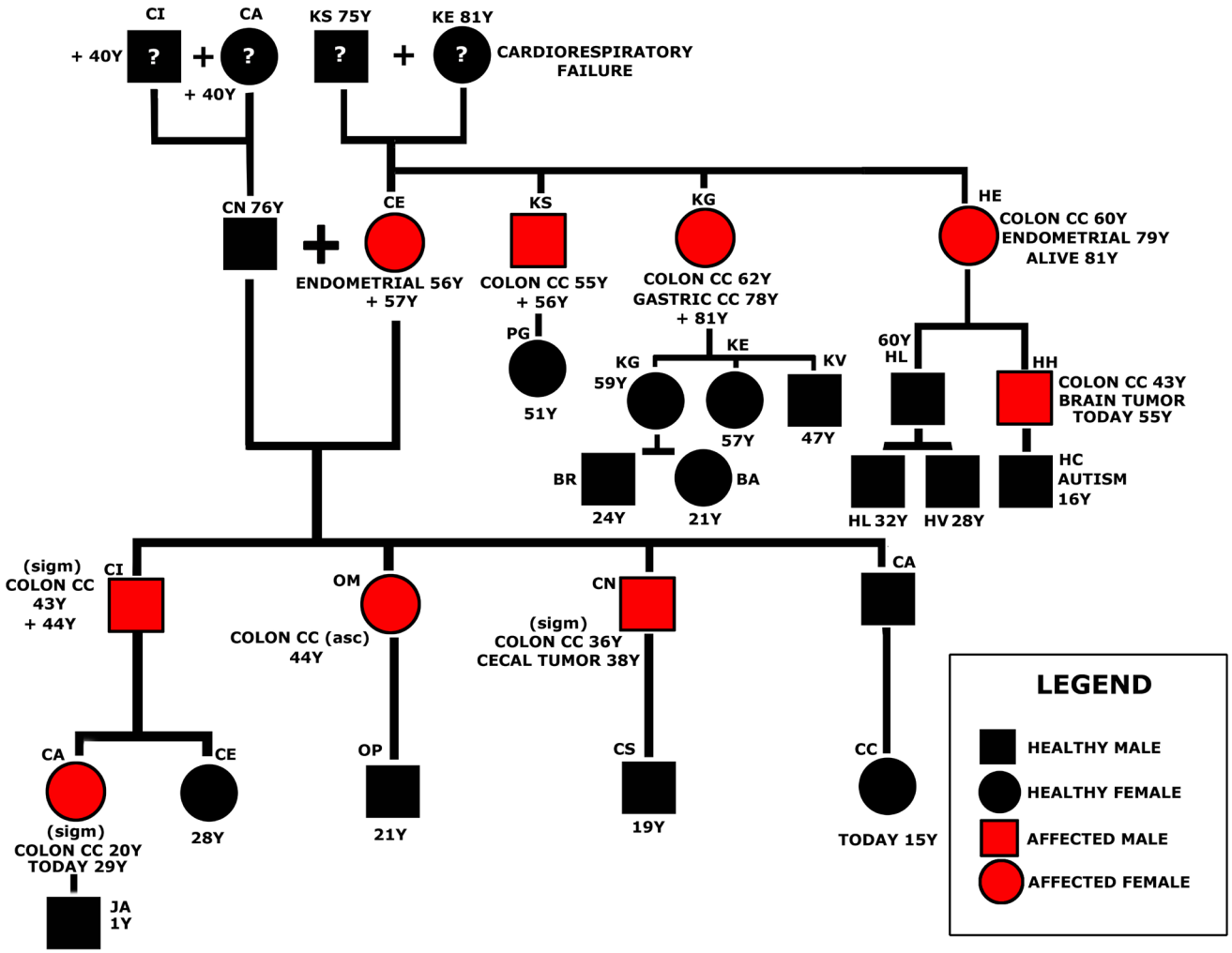

Figure 1. The healthy and affected individuals of this family with the specific malignant tumors occurred

investigation consisted on irigography which suspected a cecal tumor, malignant, because of the filling defect in cecal lumen; for this tumor was performed a right hemicolectomy with end-to-end ileo-transversostomy; but the pathology diagnosed a cecal lipoma. The patient diagnosed with a single endometrial cancer died because of cancer disease one year later. Five members of this family are still alive. The patient OM suffered also a bilateral adnexectomy because of ovarian cyst and an extrauterine pregnancy and was diagnosed with gastritis Helicobacter pylori positive; she is submitted to a yearly medical control especially for a possible another large bowel, genital, gastric or renal cancer. The patient CN was diagnosed with renal stones and is under medical treatment. All the patients figured in black are at the moment of this study without any simptom, but many of them refused investigations.

Discussions

It is considered that Lynch syndrome is the cause of 3% (4,250) of an approximately number of 143,000 individuals diagnosed each year with a colorectal cancer (Coates *et al* 2011). The risk of developing colorectal cancer is increased 2 to 3 times in people with a first-degree relative who has had a colorectal cancer, compared to individuals without family history; in case that the affected relative was diagnosed at a young age or there is more than one affected relative, the risk is increased 3 to 6 times that of the general population (Johns and Houlston 2001; Butterworth *et al* 2006). Around 20% of all patients diagnosed with colorectal cancer have a close relative affected by the disease (Lynch and de la Chapelle 2003).

The Lynch syndrome may be divided in two subdivisions, Lynch I and Lynch II syndromes. Lynch I syndrome is a hereditary site specific colorectal cancer, meanwhile Lynch II syndrome is characterized by an increased risk of colorectal cancers and extracolonic cancers. Our family may be incorporated in a Lynch II syndrome, because of the associated cancers of HNPCC (endometrial cancer in two women, one of them being the second malignant tumor, and a gastric cancer, also the second malignant primary in another woman). The risk of colorectal cancer in general population is 2%, meanwhile in patients with Lynch syndrome is over 80% (Dinh *et al* 2011). The most frequently types of other cancers are endometrial, ovarian and gastric cancers; also may appear cancers of the small intestine, hepatobiliary tract, urinary tract, brain, and skin. Lynch syndrome is the most common form of hereditary colorectal cancer (Lynch and Lynch 2000). Risk of endometrial cancer in women with Lynch syndrome is as high as the risk of colorectal cancer (Manchanda *et al* 2009). In general population the lifetime risk for endometrial cancer is 1.5%, while in women diagnosed with Lynch syndrome is up to 71% (Dinh *et al* 2011). Other authors observed lower percentages of lifetime risk of colorectal cancers in men

and women with MMR mutations (Hampel *et al* 2005; Dunlop *et al* 1997). Colon cancers in Lynch syndrome are most likely to develop in the right side, frequently with mucinous or signet ring cells, having peripheric lymphoid aggregates and/or lymphocytes infiltrating the tumor, and show an elevated frequency of microsatellite instability (Lynch *et al* 2009). In addition, in Lynch syndrome cancer is more likely to be diagnosed at a young age (45 years), as compared with the average age of 72 for a new diagnosis of colorectal cancer in the general population. The pacients having a Lynch syndrome are predisposed to develop a second primary cancer, within 15 years up to 50% will develop a new one, compared with a 5% risk in general population for multiple primaries (Strafford 2012).

For colorectal cancers there were explained specific pathways which are essential to their development, implying numerous mutations acquired in multiple genes that controle cell growth and differentiation (Fearon and Vogelstein 1990). The human genome has many strategies in order to protect large bowel epithelial stem cells to accumulate genomic errors. In colon cancer, three distinct pathways of genomic instability have been recognized: the chromosomal instability (CIN), microsatellite instability (MSI), and CpG Island Methylator Phenotype (CIMP) pathways (Pino and Chung 2010).

Tumorigenesis in autosomal dominant familial adenomatous polyposis (FAP) is caused by mutations in the tumor supessor APC gene located on long arm (q) of chromosome 5 (5q 21-22; Nishisho *et al* 1991) with an increased risk to develop colorectal cancer, and in autosomal recessive MUTYH-associated polyposis (MAP) gene, which is located on the short (p) arm of chromosome 1 (1p 34.3 - 32.1), caused by mutations of MUTYH glycosylase (involved in oxidative DNA damage repair and linked with predisposition to colon and gastric cancer), both of them acting through the CIN pathway (Lindor 2009). In Lynch syndrome is involved the MSI pathway, caused by mutations in the mismatch repair (MMR) genes, MSI being also implicated in up to 15% of sporadic colorectal cancers through gene inactivation resulting from hypermethylation of the promoter region (Gazzoli *et al* 2002). The CIMP pathway is linked with hyperplastic polyposis and development of colorectal cancers from serrated polyps, with somatic mutations of BRAF (proto-oncogene B-Raf, involved in directing cell growth), implicated in many cancers (Davies *et al* 2002), including 5% of colorectal cancers (Namba *et al* 2003) and MLH1 promoter methylation in the tumour (Jass 2007). The methylation in CIMP tumours does not necessarily abolish DNA mismatch repair, this will not be associated with MSI (Peltomäki 2005). Another category, familial colorectal cancer type X (FCCTX) concerns the families which fulfill the Amsterdam criteria 1 but have microsatellite-stable tumors, showing a lower risk to develop cancer than the patients with Lynch syndrome (Lindor *et al* 2005). But not all families classified as FCCTX necessary share a common genetic predisposition (Woods *et al* 2010).

In Lynch syndromes the particularity is the microsatellite instability (MSI). MSI are repeated small sequences of a variable number from 1 to 6 base pairs, suitable for DNA replication errors (increase or decrease in number) in case of the defects in mismatch repair genes (MMR genes). MSI pathway is implicated in more than 95% of patients with Lynch syndrome, being the hallmark of it, in contrast with it's presence in only 15-20% of patients with sporadic colorectal cancers (Geiersbach and Samowitz 2011). The known MMR genes are: MSH2 (mutS homolog 2) on chromosome 2p16; MLH1 (mutL homolog 1) on chromosome 3p21; MSH6 (mutS homolog 6) on chromosome 2p16; PMS2 (postmeiotic segregation 2) on chromosome 7p22; and EPCAM or TACSTD1 gene, which is responsible for a small percentage of HNPCC cases, it's deletion mutations inactivate MSH2 (Kovacs *et al* 2009; Ligtenberg *et al* 2009). These genes encode for MMR proteins that correct base mismatches, small insertions/deletions that occur during DNA replication. Their mutations in Lynch syndrome individuals are responsable for the microsatellite instability observed in tumor cells. Approximately 500 different HNPCC-associated MMR gene mutations are known (Peltomäki 2005) that primarily involve MLH1 (approximately 50%). MLH1 and MSH2 mutations account for about 90% of Lynch syndrome cases; MHS6 accounts for about 7-10% of cases; PMS2 is found in less than 5% of cases; when MSH2 protein is absent by immunohistochemistry on tumor tissue but genetic testing of the MSH2 gene is normal, an EPCAM mutation is responsible in 25% of cases (Niessen *et al* 2009; Rumilla *et al* 2011). Constitutional MSH6 mutations are linked with distal colorectal cancers and with endometrial cancer (Wijnen *et al* 1999; Berends *et al* 2002); constitutional mutations of both MSH6 and PMS2 are characterized by reduced penetrance. Nowadays it is recognized that Turcot syndrome and Muir-Torre syndrome are variants of Lynch syndrome. The Turcot syndrome is characterized by malignant brain tumors, especially astrocytoma and glioblastoma; the Muir-Torre syndrome consists of sebaceous tumors, both benign and malignant (adenomas, carcinomas and epitheliomas), keratoacantomas and at least one visceral malignancy, the most common being colorectal, followed by genitourinary cancers (with a more indolent course). Muir-Torre syndrome is a rare disorder, with an autosomal dominant inheritance, often associated with germline mutations in the MSH2, and the MLH1 genes (Hare *et al* 2008). A defect in MMR is not manifest until both alleles of an MMR gene are inactivated (Geiersbach and Samowitz 2011). In an affected individual with Lynch syndrome one allele suffered mutations, but it is considered that is required a second hit on the other allele before the defect in MMR becomes evident. Inactivation of the remaining wild-type allele can occur by a variety of mechanisms, including deletion, gene conversion, methylation, or point mutation, which may be the least common (Boland and Shike 2010)

In 1990 were established the Amsterdam criteria for considering a tumor of HNPCC syndrome origin. There must be at least 3 relatives of that patient with colorectal cancer: one relative has to be a first-degree relative of the other two; there must be at least two successive generations affected; at least one of the relatives with colorectal cancer must be diagnosed before age 50 years; the FAP syndrome must be excluded and the tumors have to be verified histologically (Vasen *et al* 1991). We consider that our family described here respects the Amsterdam criteria I. The Amsterdam criteria II (1998) introduced the Lynch-associated tumors (Vasen *et al* 1999), along with the other Amsterdam criteria. The modified Amsterdam criteria were suitable for small families in which are sufficient two cases of colorectal cancer in first-degree relatives in at least two generations and a third relative either with an endometrial cancer or an early onset

cancer. In 1996 the Bethesda Guidelines (Rodriguez-Bigas *et al* 1997) aimed to incorporate MSI and immunohistochemistry (IHC) testing to improve the identification of cases with delayed onset and/or weak family history (Bozzao *et al* 2011). It was stated that the microsatellite instability has to be tested for: members of the families that meet the Amsterdam criteria; if f there is a presence of multiple synchronous or metachronous Lynch syndrome-associated cancers, regardless of age; in case of individuals with colorectal cancer and a first-degree relative with Lynch syndrome-associated cancer, but diagnosed before age 45 years, or an adenoma diagnosed before age 40 years; if there are individuals with colorectal or endometrial cancer diagnosed before age 45 years; in the cases of individuals with right-sided colorectal cancer with histopathological undifferentiated pattern diagnosed before age 45 years; if there are individuals with colorectal cancer with signet ring histology (more than 50% of cells) diagnosed before age 45 years; in individuals with adenomas diagnosed before age 40 years.

Revised Bethesda Criteria (Umar *et al* 2004) implied a diagnosis of a colorectal cancer before age 50, the presence of colorectal cancers (either synchronous or metachronous), or colorectal cancer with another HNPCC-associated tumors not linked with age, microsatellite instability of the tumors before 60 years, at least one first-degree relative with a Lynch syndrome-related tumor, from which one was diagnosed before 50 years of age, at least two first/second-degree relatives with Lynch syndrome-related tumors at any age.

General screening guidelines for patients with Lynch syndrome consist of prevention of colorectal, endometrial, ovarian, other gastrointestinal malignant tumors. Colorectal tumors need to perform colonoscopy every one to two years, beginning between the ages of 20 to 25 (or five years younger than the earliest age at diagnosis in the family). These guidelines are respected by some of the members of our family presented here, but not of all their relatives. Some of their close relatives do not want to perform any investigation. For genital cancers beginning between the ages of 25 to 30 it is beneficial to perform a yearly pelvic examination, Pap test, transvaginal ultrasound, endometrial biopsy, and CA-125 blood test (ovarian cancer). For gastrointestinal cancers, especially in families with members having such malignant tumors, is indicated a periodic upper endoscopy screening. In case of urinary tract cancers it is recommended a yearly urine cytology and renal imaging beginning at age 30-35. For skin tumors, due to an increased risk of Muir-Torre syndrome, it is recommended a full body dermatologic examination performed yearly. Surgery can offer options in case of an initial presence of colorectal cancer: subtotal colectomy, because of an increased frequency of metachronous cancer. In germ-line mutation carriers, in addition to cancer screening, surgical therapy proposes prophylactic colectomy as well as prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy (Lynch and Lynch 2000*).

In HNPCC multiple tumors occur more often than in those with sporadic colorectal cancers. 3-10% of malignant tumors of the large bowel occur in Lynch syndrome patients. 4% of 1298 patients with colorectal carcinoma had synchronous and metachronous carcinomas, the multiple tumors (especially metachronous) appeared more frequently in Lynch syndrome patients (Fante *et al* 1996).

In our department were surgically treated four of the members of this family (those represented in the lower part of Figure 1), none of them with multiple malignant tumors, but with multiple neoplasia of the colorectum. We do not know in fact if the parents of the first generation involved suffered with any malignant tumor. The family members which today are alive do not know, they have been told that their grandparents from their mother side had cardiovasculary diseases and died at an advanced age. Also, the grandparents from their father side died inexplicable at a young age. We may suppose a cancer or a cardiac disease. Another important aspect is that in the first affected generation the cancers were diagnosed at an age over 50 years, and the brother and a sister died one year after the diagnosis and surgical treatment, because an advanced disease. The other two sisters developed a colon cancer and an endometrial one, respectively, 5-6 years later than the members mentioned. Once the malignant tumors were cured, both developed much later (16-19 years) another primary, gastric and endometrial cancer. The sister with gastric cancer died three years after a subtotal gastrectomy. In the second generation two brothers and a sister developed colon cancer, but this time at an age below 50. In fact, it was observed a continue decrease of the age for development of a primary large bowel malignancy (from 43 years to 36 years), which will continue to decrease to a level of 20 years of age for the daughter of the eldest brother (the third generation involved with the appearance of a colon cancer). Also, the cousin (HH) was diagnosed below age of 50 years with a colon cancer, and then developed a brain tumor. In fact the youngest member of this family affected by colorectal cancer was the first one diagnosed and surgically treated in our hospital (at the age of 20 years in 2004), then it was treated her father with a sigmoid cancer (with signet ring cell carcinoma) locally advanced and then the other two (uncle and aunt of the 20 years old female).

In this familial cancer syndrome (Lynch syndrome) the sites with the most common involved organs with malignant tumors are the colorectum and the endometrium, the lifetime risk being up to 60%-80% and 40%-60%, respectively (Meyer *et al* 2009). For an ovarian cancer there is a 12% lifetime risk in women having this syndrome (Dunlop *et al* 1997; Aarnio *et al* 1999). The lifetime risk of endometrial cancer compared to the general population is twenty times increased in mutation carriers of MSH2, MSH6 and MLH1 genes, instead of a lifetime risk of only four times elevated in familial colorectal cancer families (Boilesen *et al* 2008). Approximately 25% of women with Lynch syndrome-associated colorectal cancers developed an endometrial cancer within 10 years (Obermair *et al* 2010). Women which were diagnosed with a colorectal cancer had a 1.6% risk to develop another endometrial, comparing with a risk of 23.4% of women belonging to Lynch syndrome who developed in 10 years the same malignant tumors. This is the reason for which it was suggested the concept of a "sentinel" cancer (women with Lynch syndrome have an increased risk of developing subsequent primary cancers following an initial one). There were research groups suggesting that the risk of a second primary cancer in Lynch carriers is 25% and 50% by 10 and 15 years, respectively, after diagnosis of a first cancer; a colorectal cancer may be a sentinel cancer in almost 50% of women with Lynch syndrome affected by multiple cancers, and the endometrial cancer may be the sentinel cancer in the the other 50% (Lu *et al* 2005). 7% of women. Comparing with the

patients having synchronous or metachronous colon and endometrial cancer, it was observed that 7% of women with synchronous endometrial and ovarian cancer may be incorporated in Lynch syndrome (Soliman *et al* 2005).

Conclusions

In all cancers it is important an active and long-term follow-up of the patients, but in Lynch syndrom where there is a significantly higher risk for developing metachronous lesions is crucial. The total colonoscopy and the intraoperatively examination of the entire peritoneal cavity, especially the large bowel, genital organs, stomach, kidneys, etc are mandatory for identification of possible synchronous tumors (both benign and malignant). The screening guidelines suggested in other countries are efficient in discover and treat in an useful stage the new malignant tumors occured and also may prevent , at least in part, the developemnt of other cancers. Another very important thing is the population education about all these familial syndromes and also we suggest that suspected people undergo genetic testing.

References

Aaltonen, L. A., Salovaara, R., Kristo, P., Canzian, F., Hemminki A., Peltomaki P. et al, 1998. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. New Engl J Med 338:1481-1487.

Aarnio, M., Sankila, R., Pukkala, E., Salovaara, R., Aaltonen, L.A., de la Chapelle, A. et al, 1999. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 81:214-218.

Berends, M. J., Wu, Y., Sijmons, R. H., Mensink, R. G., van der Sluis, T., Hordijk-Hos, J. M. et al, 2002. Molecular and clinical characteristics of MSH6 variants: an analysis of 25 index carriers of a germline variant. Am J Hum Genet 70(1):26-37.

Boilesen, A. E., Bisgaard, M. L., Bernstein, I., 2008. Risk of gynecologic cancers in Danish hereditary non-polyposis colorectal cancer families. Acta Obstet Gynecol Scand 87(11):1129-35.

Boland, C. R., Shike, M., 2010. Report from the Jerusalem workshop on Lynch syndrome-hereditary nonpolyposis colorectal cancer. Gastroenterology 138(7):2197 e2191–2197.

Bozzao, C., Lastella, P., and Stella, A., 2011. Anticipation in Lynch Syndrome: Where We Are Where We Go. Curr Genomics 12(7):451–465.

Butterworth, A. S., Higgins, J. P., Pharoah, P., 2006. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 42(2):216-227.

Coates, R., Williams, M., Melillo, S., Gudgeon, J., 2011. Genetic testing for lynch syndrome in individuals newly diagnosed with colorectal cancer to reduce morbidity and mortality from colorectal cancer in their relatives. PLoS Curr 6;3:RRN1246.

Davies, H., Bignell, G. R., Cox, C., Stephens, P., Edkins, S., Clegg, S., et al, 2002. "Mutations of the BRAF gene in human cancer". Nature 417(6892):949–54.

Dinh, T. A., Rosner, B. I., Atwood, J. C., Boland, C. R., Syngal, S., Vasen, H. F. et al, 2011. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res (Phila) 4(1):9-22.

Dunlop, M. G., Farrington, S. M., Carothers, A. D., Wyllie, A. H., Sharp, L., Burn, J. et al, 1997. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 6(1):105-10.

Fante, R., Roncucci, L., Di Gregorio, C., Tamassia, M. G., Losi, L., Benatti, P. et al, 1996. Frequency and clinical features of multiple tumors of the large bowel in the general population and in patients with hereditary colorectal carcinoma. Cancer 77(10):2013-21.

Fearon, E. R., Vogelstein, B., 1990. A genetic model for colorectal tumorigenesis. Cell 1;61(5):759–767.

Gazzoli, I., Loda, M., Garber, J., Syngal, S., Kolodner, R. D., 2002. A hereditary nonpolyposis colorectal carcinoma case associated with hypermethylation of the MLH1 gene in normal tissue and loss of heterozygosity of the unmethylated allele in the resulting microsatellite instability-high tumor. Cancer Res 62(14):3925-8.

Geiersbach, K. B. and Samowitz, W. S., 2011. Microsatellite Instability and Colorectal Cancer. Arch Pathol Lab Med—Vol 135:1269-1277

Hampel, H., Stephens, J. A., Pukkala, E., Sankila R., Aaltonen, L. A., Mecklin, J. P. et al, 2005. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology 129(2):415–21.

Hare, H. H., Mahendraker, N., Sarwate, S., Tangella, K., 2008. Muir-Torre syndrome: a rare but important disorder. Cutis 82(4):252–256.

Jass, J. R., 2007. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 50:113–30.

Jemal, A., Murray, T., Ward, E., Samuels, A., Tiwari, R. C., Ghafoor, A., et al, 2005. Cancer statistics, 2005. CA Cancer J Clin 55(1):10-30.

Jemal, A., Siegel, R., Xu, J., Ward, E., 2010. Cancer Statistics, 2010. CA Cancer J Clin 60:277–300

Johns, L. E., Houlston, R. S., 2001. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 96(10):2992-3003.

Katballe, N., Christensen, M., Wikman, F. P., Orntoft, T. F., Laurberg, S., 2002. Frequency of hereditary non-polyposis colorectal cancer in Danish colorectal cancer patients. Gut 50:43-51.

Kovacs, M. E., Papp, J., Szentirmay, Z., Otto, S., Olah, E., 2009. Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. Hum Mutat 30(2):197-203.

Ligtenberg, M. J., Kuiper, R. P., Chan, T. L., Goossens, M., Hebeda, K. M., Voorendt, et al, 2009. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet 41(1):112-7.

Lindor, N. M., 2009. Hereditary colorectal cancer: MYH-associated polyposis and other newly identified disorders. Best Pract Res Clin Gastroenterol 23(1):75-87.

Lindor, N. M., Rabe, K., Petersen, G. M., Haile, R., Casey, G., Baron, J,. et al, 2005. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA 293(16):1979-85.

Lynch, H. T., 1999. Hereditary nonpolyposis colorectal cancer (HNPCC). Cytogenet Cell Genet 86:130-135.

Lynch, H. T., de la Chapelle, A., 2003. Hereditary colorectal cancer. N Engl J Med 348(10):919-932.

Lynch, H. T., Lynch, J. F., 2000. Hereditary nonpolyposis colorectal cancer. Semin Surg Oncol 18(4):305-13.

Lynch, H. T., Lynch, J., 2000*. Lynch syndrome: genetics, natural history, genetic counseling, and prevention. J Clin Oncol 18(21 Suppl):19S-31S.

Lynch, H. T., Lynch, J. F., Attard, T. A., 2009. Diagnosis and management of hereditary colorectal cancer syndromes: Lynch syndrome as a model. CMAJ 181(5):273-280.

Lynch, H. T., Lynch, P. M., Lanspa, S. J., Snyder, C. L., Lynch, J. F., Boland, C. R., 2009. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clinical Genetics 76(1):1–18.

Lu, K. H., Dinh, M., Kohlmann, W., Watson, P., Green, J., Syngal, et al, 2005. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol 105(3):569-74.

Manchanda, R., Menon, U., Michaelson-Cohen, R., Beller, U., Jacobs, I., 2009. Hereditary non-polyposis colorectal cancer or Lynch syndrome: the gynaecological perspective. Curr Opin Obstet Gynecol 21(1):31-8.

Marra, G., Boland, C. R., 1995. Hereditary nonpolyposis colorectal cancer: the syndrome, the genes, and historical perspectives. J Natl Cancer Inst 87:1114-1125.

Meyer, L. A., Broaddus, R. R., Lu, K. H., 2009. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control 16(1):14-22.

Namba, H., Nakashima, M., Hayashi, T., Hayashida, N., Maeda, S., Rogounovitch, T. I., et al, 2003. "Clinical implication of hot spot BRAF mutation, V599E, in papillary thyroid cancers". J. Clin. Endocrinol. Metab. 88 (9): 4393–7.

Niessen, R. C., Hofstra, R. M., Westers, H., Ligtenberg, M. J., Kooi, K., Jager, P. O., et al., 2009. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. Genes chromosomes Cancer 48(8):737-44.

Nishisho, I., Nakamura, Y., Miyoshi, Y., Miki, Y., Ando, H., Horii, A., et al, 1991. "Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients". Science 253 (5020): 665–9.

Obermair, A., Youlden, D. R., Young, J. P., Lindor, N. M., Baron, J. A., Newcomb, P., et al, 2010. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer 2010 127(11):2678-84.

Peltomäki, P., 2005. Lynch syndrome genes. Fam Cancer 4(3):227-32.

Pino, M. S., Chung, D. C., 2010. The chromosomal instability pathway in colon cancer. Gastroenterology 138(6):2059–2072.

Ponz de Leon, M., Pedroni, M., Benatti, P., Percesepe, A., Di Gregorio, C., Foroni M., et al, 1999. Hereditary colorectal cancer in the general population: from cancer registration to molecular diagnosis. Gut 45:32-38.

Raedle, J., Schaffner, M., Esser, N., Sahm, S., Trojan, J., Kriener, S., et al, 2002. Frequency of the amsterdam criteria in a regional german cohort of patients with colorectal cancer. Z Gastroenterol 40:561-568.

Rodriguez-Bigas, M. A., Boland, C. R., Hamilton, S. R., Henson, D. E., Jass, J. R., Khan, P. M., et al, 1997. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 89(23):1758-62.

Rumilla, K., Schowalter, K. V., Lindor, N. M., Thomas, B. C., Mensink, K. A., Gallinger, S., et al., 2011. Frequency of deletions of EPCAM (TACSTD1) in MSH2-associated lynch syndrome cases. J Mol Diagn 13(1):93-9.

Siegel, R., Ward, E., Brawley, O., Jemal, A., 2011. Cancer Statistics, 2011. The Impact of Eliminating Socioeconomic and Racial Disparities on Premature Cancer Deaths CA Cancer J Clin 61:212-236.

Soliman, P. T., Broaddus, R. R., Schmeler, K. M., Daniels, M. S., Gonzalez, D., Slomovitz, B. M., et al, 2005. Women With Synchronous Primary Cancers of the Endometrium and Ovary: Do They Have Lynch Syndrome? J Clin Oncol 23(36):9344-9350.

Strafford, JC., 2012 Genetic testing for Lynch syndrome, an inherited cancer of the bowel, endometrium, and ovary. Reviews in Obstetrics&Gynecology 5(1):42-49.

Umar, A., Boland, C. R., Terdiman, J. P., Syngal, S., de la Chapelle, A., Rüschoff, J., et al, 2004. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J. Natl. Cancer Inst 96:261–268.

Vasen, H. F., Mecklin, J. P., Khan, P. M., Lynch, H. T., 1991. The International Collaborative Group on hereditary non-polyposis colorectal cancer (ICG-HNPCC). Dis Colon Rectum 34(5):424–425.

Vasen, H. F., Watson, P., Mecklin, J. P., Lynch, H. T., 1999. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 116(6):1453–1456.

Wijnen, J., de Leeuw, W., Vasen, H., van der Klift, H., Møller, P., Stormorken, A., et al, 1999. Familial endometrial cancer in female carriers of MSH6 germline mutations. Nat Genet 23(2):142-4.

Woods, M. O., Younghusband, H. B., Parfrey, P. S., Gallinger, S., McLaughlin, J., Dicks, E., et al, 2010. The genetic basis of colorectal cancer in a population-based incident cohort with a high rate of familial disease. Gut 59(10): 1369–1377.

Authors

•Daciana N. Chirilă, „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Department of Surgery, 5th Surgical Clinic, 11th Tăbăcarilor Street, 400139, Cluj-Napoca, Romania, EU, e-mail: dacianachirila@gmail.com

•Nicolae A. Turdeanu, „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Department of Surgery, 5th Surgical Clinic, 11th Tăbăcarilor Street, 400139, Cluj-Napoca, Romania, EU, e-mail: turdeanustela@yahoo.com

•Nicolae A. Constantea, „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Department of Surgery, 5th Surgical Clinic, 11th Tăbăcarilor Street, 400139, Cluj-Napoca, Romania, EU, e-mail: nicuconstantea@yahoo.com

•Radu Popp: Department of Genetics "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, romania, EU, e-mail: radupopp2001@yahoo.com

•Ovidiu Balacescu: Functional Genomics, Proteomics and Experimental Pathology Laboratory, The Oncology Institute „Ion Chiricuţă" Cluj-Napoca, Romania, EU, e-mail: obalacescu@yahoo.com

•Tudor R. Pop: „Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Department of Surgery, 5th Surgical Clinic, 11th Tabacarilor Street, 400139, Romania, EU, e-mail: poptudor_2003@yahoo.com

•Cătălina I. Bungărdean: Vth County Hospital, Department of Pathology, 11th Tabacarilor Street, 400139, Romania, EU, e-mail: mariabun2002@yahoo.com

•Ciuce Constantin, „Iuliu Haţieganu" University of Medicine andPharmacy, Cluj-Napoca, Department of Surgery, 1st Surgical Clinic, 3-5th Clinicilor Street, 400139, Cluj-Napoca, Romania, EU, e-mail: cciuce@umfcluj.ro

Citation	Chirilă, D. N., Turdeanu, N. A., Constantea, N. A., Popp, R., Bălăcescu, O., Pop, T. R., Bungărdean, C. I., Ciuce, C., 2012. Family with a multiple cancer syndrome. HVM Bioflux 4(3):90-96.
Editor	Ştefan C. Vesa
Received	30 October 2012
Accepted	28 November 2012
Published Online	28 November 2012
Funding	None reported
Conflicts/ Competing Interests	None reported