**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 83186

**Manuscript Type:** MINIREVIEWS

**Synchronous manifestation of colorectal cancer and intraductal papillary mucinous neoplasms**

Mirchev MB *et al*. Synchronous CRC and IPMN

Milko Bozhidarov Mirchev, Irina Boeva, Monika Peshevska-Sekulovska, Veselin Stoitsov, Milena Peruhova

**Milko Bozhidarov Mirchev, Irina Boeva, Veselin Stoitsov, Milena Peruhova,** Department of Gastroenterology, Heart and Brain Hospital, Burgas 8000, Bulgaria

**Monika Peshevska-Sekulovska,** Department of Gastroenterology, University Hospital Lozenetz, Sofia 1407, Bulgaria

**Author contributions:** Mirchev M and Peruhova M wrote the majority of the manuscript; Boeva I and Peshevska-Sekulovska M prepared the figures and tables; Stoitsov V provided critical revision, designed the outline of the manuscript, and coordinated the writing of the paper.

**Corresponding author: Milena Peruhova, MD, Assistant Professor,** Department of Gastroenterology, Heart and Brain Hospital, Zdrave 1 st, Burgas 8000, Bulgaria. mperuhova@gmail.com

**Received:** January 10, 2023

**Revised:** February 26, 2023

**Accepted:** April 17, 2023

**Published online:** May 26, 2023

**Abstract**

High rates of extrapancreatic malignancies, in particular colorectal cancer (CRC), have been detected in patients with intraductal papillary mucinous neoplasm (IPMN). So far, there is no distinct explanation in the literature for the development of secondary or synchronous malignancies in patients with IPMN. In the past few years, some data related to common genetic alterations in IPMN and other affiliated cancers have been published. This review elucidated the association between IPMN and CRC, shedding light on the most relevant genetic alterations that may explain the possible relationship between these entities. In keeping with our findings, we suggested that once the diagnosis of IPMN is made, special consideration of CRC should be undertaken. Presently, there are no specific guidelines regarding colorectal screening programs for patients with IPMN. We recommend that patients with IPMNs are at high-risk for CRC, and a more rigorous colorectal surveillance program should be implemented.

**Key Words:** Colorectal cancer; Intraductal papillary mucinous neoplasm; Genetic alterations; Extrapancreatic malignancies; Synchronous neoplasms

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**Citation:** Mirchev MB, Boeva I, Peshevska-Sekulovska M, Stoitsov V, Peruhova M. Synchronous manifestation of colorectal cancer and intraductal papillary mucinous neoplasms. *World J Clin Cases* 2023; 11(15): 3408-3417

**URL:** https://www.wjgnet.com/2307-8960/full/v11/i15/3408.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v11.i15.3408

**Core Tip:** In this mini-review, we highlighted the genetic alterations that occur in intraductal papillary mucinous neoplasm (IPMN) and colorectal cancer to understand common genetic or epigenetic risk factors that could explain their synchronous manifestation. The process of malignant transformation in both entities is complex, but some distinctive features of IPMN lesions are linked with their genetic heterogeneity. Specific mutations in *GNAS* and *KRAS* are mainly expressed in IPMN. A significantly lower frequency of mutations is detected in other cancer-related genes, such as *SMAD4*, *PI3KCA*, *PTEN*, and *BRAF*.

**INTRODUCTION**

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is characterized histologically by a broad spectrum of transformation starting from low-grade dysplasia, moderate dysplasia, high-grade dysplasia, and invasive pancreatic carcinoma (PC)[1]. Depending on the epithelial type, IPMN has a variable prognosis with the unambiguous potential to transform into invasive PC[2].

IPMN is characterized by intraductal papillary growth and mucous secretion, which leads to ductal dilatation of the pancreas. IPMN is classified into main duct IPMN, branch duct IPMN, or mixed type IPMN and is based on anatomical involvement of the pancreatic ductal system[3]. It was estimated that the main duct type IPMN has a higher malignancy potential, with a range of 36%-100%[4]. It is important to note that even malignant IPMN can be resected and has a better prognosis compared with pancreatic ductal adenocarcinoma[5]. In the last few decades, many studies have been published representing an interesting correlation between IPMN and other malignancies, which emerge before or simultaneously with the diagnosis of IPMN. It was estimated that in patients with IPMN, the incidence of additional malignancy is in the range of 10%-52%[6].

Typically, the gastrointestinal (GI) tract is involved, with a prevalence of colon polyps and colorectal cancer (CRC) in Western countries and gastric cancer in Asian countries[7]. The incidence of synchronous CRCs and IPMN is about 3%-12% in Western countries[8]. In some publications, it was pointed out that the frequency of colonic adenomas was uncommonly higher in patients with IPMN than in those with pancreatic ductal adenocarcinoma[9].

In the last two decades, a unique carcinogenesis model for CRC has been revealed with a detailed analysis of underlying genetic and epigenetic alterations[10]. On the contrary, the mechanisms of malignant transformation in IPMN remain poorly understood. It is believed that IPMN is fundamentally characterized by a genetic lesion and that an accumulation of somatic mutations drives the histologic progression, ultimately leading to malignant transformation[11].

So far, there is no distinct explanation in the literature for the development of secondary or synchronous malignancies in patients with IPMN. In the past few years, data were published related to common genetic alterations between IPMN and other affiliated cancers[12,13]. This review elucidates the association between IPMN and CRC. We also discuss the most relevant information concerning the molecular mechanism of genetic alterations leading to the synchronous development of IPMN and CRC.

**MOLECULAR PATHWAYS OF IPMN MALIGNANT TRANSFORMATION TO PC**

Pancreatic carcinogenesis is a result of somatic and germline mutations. For instance, inactivating mutations in tumor suppressor genes *TP53*, *CDKN2A*, and *SMAD4* and activating gene mutations in the oncogene *KRAS*[14] are known contributors. Omori *et* *al*[4] investigated genetic alterations that occur in IPMN lesions leading to PC based on genetic and histologic analyses. According to the authors, there are three subtypes of malignant transformation from IPMN to PC. The first subtype is called the sequential pathway, which has a specific sequential acquisition of driver and tumor suppressor gene mutations, with frequent *GNAS* mutations that lead to PC development. The second type is called branch-off pathway, characterized by certain *KRAS* mutations that are common among PC and *GNAS* mutations that are more prevalent in IPMN. The third subtype has *de novo* driver mutations not found in concurrent IPMN and has substantial heterogeneity among early clones. Additionally, it was proven that PC resulting from the sequential or branch-off pathways has a worse prognosis compared to the *de novo* PC[15].

An interesting study by Ren *et* *al*[16] highlighted that *GNAS* and *KRAS* mutations are frequently observed in IPMN and are very specific for this entity. We want to underline that mutations in the aforementioned genes are one of the initial steps in the malignant transformation. However, this process is more complex, and additional genetic alterations, occurring in a stepwise manner, are needed to proceed with the process of malignant transformation of IPMN[17,18].

To summarize, the precise manner of malignant transformation of IPMN to PC is a more complex process due to the high genetic heterogeneity characterized by IPMN lesions (Figure 1).

**BASIC ASPECTS OF COLORECTAL CARCINOGENESIS**

CRC was one of the first genetically characterized tumors in which a stepwise progression was discovered and several molecular pathways for its formation have been proposed[19]. In the widely popular adenoma-carcinoma sequence, a gradual transition from normal colonic mucosa through aberrant crypt foci, small, medium, and large adenoma to carcinoma is accompanied by the accumulation of driver gene mutations, namely *APC*, *KRAS*, *PIK3CA*, *SMAD4*, and *TP53*[20]. This is the so-called chromosomal instability pathway, responsible for approximately 80% of sporadic CRC cases, which was proposed in the late 1990s by Fearon and Vogelstein[21].

It is believed that *APC* and *KRAS* mutations are early events in the progression from normal epithelium to adenoma, while *PIK3CA* mutation and *SMAD4* and *TP53* loss of function are late events in the adenoma-carcinoma sequence, enabling tumor cells to invade adjacent tissues and metastasize[22]. Also, the co-occurrence of *APC*, *KRAS*, and *TP53* dysfunction is associated with distant metastasis and poor outcome, whereas mutations of *PIK3CA* and *SMAD4* are absent in advanced disease[23].

An important co-player is the transforming growth factor-beta, acting in conjunction with B-catenin, which enters the cell nucleus when not regulated by the mutant *APC* gene. Together, they stimulate the Wnt pathway, leading to the induction of epithelial-mesenchymal transition and enhanced mobility and invasiveness of cells in CRC[24].

Around 5%-10% of CRC cases are due to heredity. The most common syndromes include hereditary non-polyposis CRC (HNPCC), familial adenomatous polyposis (FAP), attenuated FAP, Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome, and others[25].

The other mechanism of paramount importance for CRC formation is the microsatellite instability pathway. Microsatellites are short repetitive DNA sequences composed of 1-6 nucleotides, scattered throughout the human genome. They have no specific function but are prone to replication errors[26]. When this occurs, a special system, called the mismatch repair system (MMR), is activated and identifies and corrects base mismatches caused by DNA replication errors[27,28].

Furthermore, a third model for colorectal carcinogenesis has evolved: the CpG island methylator phenotype. It is characterized by dense promoter hypermethylation, leading to gene inactivation. Transcriptional silencing of essential tumor suppressor genes, caused by aberrant DNA methylation, could promote neoplastic growth. This mechanism is thought to be important in the serrated pathway in CRC[29].

**COMMON AND SPECIFIC GENETIC ALTERATIONS IN IPMN AND CRC**

***IPMN and Lynch syndrome/HNPCC***

Defective DNA MMR emerges from genetic or epigenetic alterations that most frequently lead to the inactivation of the genes *hMLH1* and *hMSH2*. This genetic abnormality is thought to promote tumorigenesis by the accumulation of mutations in oncogenes and tumor suppressor genes. This pathway was reported in the tumorigenesis of CRC and later in other malignancies as well[30].

HNPCC, also known as Lynch syndrome, is characterized by germline mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*)[31]. As a result of these mutations, abnormal cell growth, and tumor development occurs because of defective repair of mismatched DNA[32]. It was estimated that 2%-3% of all CRCs are caused as a result of Lynch syndrome. It is important to highlight that Lynch syndrome markedly increases the risk for various cancers, especially those of the colon and endometrium[33]. Even though families with Lynch syndrome are at higher risk of PC, a clear correlation between Lynch syndrome and IPMN has not been established yet.

To our knowledge, there are scarce data in the literature about the concomitant diagnosis of IPMN and Lynch syndrome. Only two case reports have been published so far. The first one was reported on patients with Lynch syndrome and IPMN, with a confirmed germline mutation in the *MSH2* gene. It was confirmed that both tumors (colorectal and IPMN) showed identical loss of expression of *MSH2* and *MSH6* as well as a high level of microsatellite instability. Based on this fact it can be suggested that IPMN could be part of the variations of Lynch syndrome[34].

The second case was about a patient who met Amsterdam criteria for Lynch syndrome with a germline mutation in *MSH2* and had a synchronous IPMN. More interestingly, in that case, the IPMN specimen did not demonstrate microsatellite instability and had preserved *MSH2* expression[35].

In general, both case reports provided evidence for a potential relationship between Lynch syndrome and IPMN. Emerging new approaches revealed that mutations in MMR genes could play a role in the development of IPMN.

Although the accurate nature of the relationship between IPMN and Lynch syndrome is not yet understood, an enhanced level of suspicion for patients with Lynch syndrome and concomitant pancreatic cystic lesions is warranted. Further studies have to be conducted to identify the relationship between IPMN and HNPCC (Figure 2).

***PJS and IPMN***

PJS is an autosomal dominant hereditary syndrome characterized by intestinal hamartomatous polyposis and mucocutaneous pigmentation[36]. It was established that patients with PJS have a higher risk of malignancies such as GI tumors (CRC, esophagus), and breast, ovarian and urinary cancers[37]. This syndrome is due to germline mutations in the *STK11* gene. Recently, it was discovered that this gene exerts an impact on p53-dependent apoptosis[38].

To shed light on the role of genetic alterations and molecular features of IPMN, Sato *et* *al*[39] published a comparative study analyzing 22 IPMNs among patients with and without PJS. The authors revealed that *STK11*/*LKB1* mutations were present in 100% (2/2) of samples from PJS patients *vs* only 25% (5/20) of samples from patients without PJS. In general, these data suggest that *STK11*/*LKB1* mutations could play an important role in IPMN development.

A study by Resta *et* *al*[40] observed that *STK11*/*LKB1* mutations in IPMNs among PJS patients may predispose this patient population to higher rates of progression to CRC compared to the general population. Therefore, such patients have a high risk of developing a variety of malignancies, including IPMN and CRC, and strict screening should be advised for these patients.

***FAP***

FAP is an autosomal dominant syndrome characterized by germline mutations in the *APC* gene on chromosome 5q21. This entity is associated with the development of hundreds to thousands of adenomas in the GI tract[41]. Polyps often develop at an early age and harbor a 100% lifetime risk of CRC. Patients with FAP have a high risk of developing other malignancies, including gastric, duodenal, pancreatic, and desmoid tumors[42].

IPMN is an extremely rare extracolonic manifestation associated with FAP, with few published cases in the medical literature so far. A case report by Maire *et* *al*[43] demonstrated an association between FAP and IPMN in a 41-year-old patient. The authors performed genetic analysis and found the absence of APC protein, which is typical of the adenomas in FAP patients, and wildtype *APC* in IPMN. These findings supported the idea that *APC* mutation leading to the transformation of normal mucosa into CRC could also play a role in the carcinogenesis of IPMN.

In addition to the above, another case report published by Chetty *et* *al*[44] provided a correlation between FAP and IPMN. The patient had an extracolonic manifestation IPMN of the pancreas and polypoid gastric heterotopia in the duodenum. The immunohistochemical analysis confirmed that duodenal adenomas and IPMN of the pancreas were pathogenetically related, with the IPMN being an unusual extracolonic manifestation of FAP and/or attenuated FAP.

**RELEVANT DATA CONCERNING THE ASSOCIATION BETWEEN IPMN AND CRC**

In 1999, the first study related to the concomitant manifestation of IPMN and other extrapancreatic malignancies (EPMs) was published. Afterward, many additional studies were conducted to determine the frequency of prevalent or incident EPMs in patients with IPMN[12]. The results of these publications indicated that the frequency of EPM was around 24.6%-39.0%[7,45]. However, the majority of these studies were retrospective, based on a small group of patients, or featured a recruitment bias. Over the last few years, several meta-analyses and large studies confirmed an increased frequency of GI malignancy in IPMN patients in comparison to the general population. Thus, most research teams suggest special CRC surveillance programs for these patients.

A large meta-analysis, reviewing 16 studies and a total of 8240 patients, was published in 2022. The authors quantified the association between IPMN and EPM. They found that compared to the general population patients with IPMNs faced a greater risk of EPM. The subgroup analysis for GI malignancies in patients harboring IPMN provided an odds ratio of 12.9[46]. In 2022, Zelnik *et* *al*[47]published a matched cross-sectional historical study comparing the prevalence of colorectal polyps and CRC among 310 IPMN patients in comparison to sex- and age-matched middle-risk patients. The authors established a significantly higher prevalence of polyps with advanced dysplasia and CRC in the IPMN group than in matched controls, while the occurrence of polyps was similar in both groups. This study had some limitations such as a lack of IPMN histopathological specimens, genetic tests to determine shared molecular mechanisms for IPMN and CRC, and the absence of information regarding the time relationship between the appearance of findings in the pancreas and colon[47].

A study from the Mayo Clinic in 2010 confirmed that patients with IPMN had an increased risk of harboring EPM, in particular, CRC. In addition, the authors observed an increased incidence of colorectal adenomas in the IPMN group. The association between IPMN and colorectal polyps still remains uncertain. A prospective study published by Panic *et* *al*[48] suggested that the elevated risk of CRC among patients with IPMN was not related to accelerated adenoma formation.

In 2006, Eguchi *et* *al*[49] investigated the incidence of synchronous or metachronous extrapancreatic cancer among 69 patients who underwent surgery for IPMN. The authors reported that CRC occurred 5.37 times more frequently in IPMN patients than in the general population. In a population-based study, Rial *et* *al*[45] reported a 1.66 times higher rate of CRC in patients with invasive IPMN compared to the general population.

More recently, Larghi *et* *al*[50] published a multicentric study that included 390 IPMN patients. The authors reported an increased prevalence of EPM, notably for CRC and thyroid cancer. The reported incidence of EPM was 23.6% overall and 12.6% for CRC. A single-center study conducted by Panic *et* *al*[48] on 198 patients with IPMN sought to find any EPMs diagnosed previously, synchronously, or after the IPMN diagnosis. One of the frequently diagnosed EPMs was CRC (12 patients, 6.1%).

Another population-based study published in 2019 analyzed a diverse patient population from a large geographic area. The results confirmed that patients with IPMN were more likely to acquire EPM than the general population. The authors concluded that the advanced IPMN stage and the short latency period over which the second neoplasm developed were predictors of higher mortality[51].

Despite all these findings, it is still debatable whether there is a clear association between IPMN and CRC. In a critical systematic review of 15 studies from 2015, Pugliese *et* *al*[52] highlighted that the majority of available studies relied on weak levels of evidence and were retrospective. The authors concluded that the available data were not unanimous. A large European multicentric observational study questioned the significant association between CRC and IPMN, raising the question of whether IPMNs are a risk factor for the emergence of EPMs[53]. Analyzing data from a 5-year follow-up of 51 resected IPMN cases, Kato *et* *al*[54] determined that the EPM risk differed significantly in different types of IPMNs. The researchers established a 4-fold higher prevalence of ЕРM for malignant IPMN cases, while benign cases featured a similar risk to the general population. Another observational study focused on side branch IPMN did not show a strong correlation between IPMNs and EPM development (Table 1)[54].

Detection of EPM may be explained by repeated imaging for IPMN surveillance. This could lead to incidental malignancy detection. Common immunological, environmental, or hereditary factors are also potential explanations[47].

Patients with benign IPMN have a lower frequency of EPM compared with patients with malignant IPMN. Thus, the precise histological assessment of IPMN lesions could be a useful tool to assess the potential EPM incidence in IPMN patients and thus improve patient management[55].

The correlation between IPMN and CRC has already been confirmed for advanced IPMN cases. The relevant data suggest a significant contrast in EPM risk for different IPMN groups. It is still unclear what type of follow-up to identify EPMs is recommended for IPMN patients who have undergone resection and those who have not. Most of the authors find it reasonable to conduct GI malignancy screening, including colonoscopy for patients harboring IPMN[56,57].

**DISCUSSION**

In the past few decades, the increased number of imaging studies in IPMN surveillance may have contributed to the high rates of incidental malignancy detection, in particular CRC[7]. Regarding the low incidence of synchronous clinical presentation of IPMN and CRC, comprehensive surveillance protocols and follow-up duration or time of screening initiation have not been established. Of course, factors such as age, female sex, and White race are thought to be risk factors for these entities[7,45].Additionally, the prognosis for patients with synchronous benign IPMN and EPM is notably better compared to those with malignant IPMN[12].It is of great importance for potential subjects for surveillance to be detected on time. In situations when patients have been diagnosed with IPMN, detailed personal and family histories should be obtained. Patients diagnosed with IPMN without a colonoscopy are indicated for this procedure because of the increased risk for associated colonic neoplasms.

A special emphasis should be placed on patients with hereditary syndromes such as PJS, Lynch syndrome, and FAP for active surveillance based on the established data related to their higher rate of association with the development of colonic and extracolonic malignancy[58].

In this review, we highlighted the genetic alterations that occur in IPMN and CRC and discussed common genetic or epigenetic risk factors that could explain their synchronous manifestation. Of course, the process of malignant transformation in both entities is complex. The carcinogenic course of IPMNs and adenomatous colorectal polyps is similar. Both entities are characterized by malignant transformation from adenoma with low-grade dysplasia through adenoma with high-grade dysplasia to an invasive tumor.

Some distinctive features of IPMNs are linked with their genetic heterogeneity. Specific mutations in the *GNAS* and *KRAS* genes are primarily expressed in IPMN. It must be highlighted that mutations in *GNAS* are found in 40%-70% of IPMNs, and a significantly lower frequency of mutations is detected in other cancer-related genes, such as *SMAD4*, *PI3KCA*, *PTEN*, and *BRAF*[59].

On the other hand, the genetics of CRC is associated with stepwise progression accompanied by mutations in the *APC*, *KRAS*, *PIK3CA*, *SMAD4*, and *TP53* genes. Unfortunately, the exact mechanism of the frequent development of synchronous IPMN and CRC is unknown. This process could be related to common environmental cancer-risk factors and genetic/epigenetic alterations that lead to common pathways of malignant transformation.

**CONCLUSION**

There is a significantly increased prevalence of CRC in patients with IPMN compared to the average population. Unfortunately, there are scarce data aimed at elucidating the molecular mechanisms leading to CRC development among patients with IPMN. More studies are needed to clarify the underlying pathophysiology and common genetic events shared between these two lesions.

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**Footnotes**

**Conflict-of-interest statement:** All the authors report having no relevant conflicts of interest for this article.

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**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** January 10, 2023

**First decision:** February 8, 2023

**Article in press:** April 17, 2023

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Bulgaria

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Emran TB, Bangladesh; Fujimori S, Japan **S-Editor:** Li L **L-Editor:** Filipodia **P-Editor:** Yu HG

 **Figure Legends**



**Figure 1 Gene mutations in different intraductal papillary mucinous neoplasm tumorigenesis pathways.** IPMN: Intraductal papillary mucinous neoplasm.



**Figure 2 Mutations in carcinogenesis of intraductal papillary mucinous neoplasm and colorectal cancer.** A: The proposed model of progression pathways during carcinogenesis of intraductal papillary mucinous neoplasm (IPMN). The light circles, triangles, pentagons, and rectangles denote the diversity of precursors; B: The precursors include pancreatic intraepithelial neoplasia and incipient IPMN, with a distinct set of driver mutations (*KRAS* and *GNAS*). CRC: Colorectal cancer; PDA: Pancreatic ductal adenocarcinoma.

**Table 1 Prevalence of extrapancreatic neoplasms and colorectal cancer and intraductal papillary mucinous neoplasm patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study design** | **Year** | **Patients** | **Prevalence of EPM, %** | **Prevalence of CRC, %** |
| Zelnik *et* *al*[47] | Cross-sectional historical study | 2022 | 310 | NA | 5.2 |
| Panic *et* *al*[48] | Single-center study | 2018 | 198 | 31.8 | 6.1 |
| Larghi *et* *al*[50] | Multicentric study | 2013 | 198 | 23.6 | 12.4 |
| Lubezky *et* *al*[59] | Retrospective study | 2012 | 82 | 20.0 | 31.0 |
| Reid-Lombardo *et* *al*[9] | Retrospective study | 2010 | 471 | 52.0 | 4.0 |
| Yoon *et* *al*[13] | Retrospective study | 2010 | 210 | 33.8 | 7.0 |
| Riall *et* *al*[45] | Population-based study | 2007 | 992 | 10.0 | 3.0 |
| Huang *et* *al*[51] | Population-based study | 2019 | 2850 | 44.1 | 6.8 |
| Eguchi *et* *al*[49] | Retrospective study | 2006 | 69 | 28.0 | 12.0 |

CRC: Colorectal cancer; EPM: Extrapancreatic malignancy; NA: Not available.



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