Kell-e félnünk a malignitástól gyermekkori IBD-ben?

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Jogos-e a probléma felvetés?

- 25% IBD gyermekkorban indul
- Hosszabb időt töltenek a betegséggel
- Betegségük kiterjedtebb és agresszívebb, mint a felnőttkori IBD
- Több immunszupprimáns és egyéb kezelést igényelnek

Kell-e attól félnünk, hogy IBD-s gyermekben malignitás alakul ki?

Kell-e attól félnünk, hogy gyermekkorban induló IBD-ben később nagyobb eséllyel alakul ki malignitás?

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- emésztőszervi

- extraintesztinális

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- a betegség miatt

- az alkalmazott kezelések miatt

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- az alkalmazott kezelések miatt
  - **hatóanyag**
  - **expozíció ideje**

Kórtan: krónikus gyulladás - malignitás

A gyulladás befolyásolja:

- DNS metlációt
- mikroszatellita stabilitiást

A gyulladásos mechanizmusokban aktív cyclooxygenase 2 befolyásolja:

- sejtpoliferációt, apoptózist
- aneuploiditás arányát
- angiogenezist

Reaktív oxigén gyökök módosítják:

- TNF, IL1, IL6, IL12, IL13, IL17, IL22, és IL23 expressziót

Tumorok 85%-ában p53 szupresszált, de a nem tumoros gyulladásban is 50%

Kell-e attól félnünk, hogy IBD-s gyermekben malignitás alakul ki?

- Krónikus gyulladás okozta adenocarcinoma
- haematológiai malignitás (EBV-HSTCL)
- bőrgyógyászati malignitások
- cervix-carcinoma

} Azathioprin asszociáció

Kell-e attól félnünk, hogy IBDs gyermekben malignitás alakul ki?

Beválogatási kritériumok:

Gyermek IBD

19 éves kor alatt diagnosztizált malignitás vagy mortalitás

Esetszám: 44

Malignitás: 18

Mortalitás: 31 (5 malignitás miatt)

TABLE 1. National Pediatric Gastroenterologists or Pediatric Gastroenterology Centers Taking Care of Pediatric Patients with IBD with Percentage of Active Response; Patient Numbers (Mortality and/or Cancer) per Country, During 2006–2011

Country	Pediatric Gastroenterologists or Centers Treating Patients with PIBD per Country	Percentage of Pediatric Gastroenterologist Who Actively Replied, %	Total No. of Patients (n = 44)	Mortality Cases per Country	Cancer Cases per Country
Germany	145 ped GIs	70	8	6	3
England	75 ped GIs	NA	4	4	1
Wales	4 ped GIs	100	1	0	1
Scotland	10 ped GIs	100	2	1	2
Spain	115 ped GIs	90	4	3	1
Sweden	21 regions	62	4	3	1
The Netherlands	35 ped GIs	100	3	1	2
Poland	16 centers	100	3	3	1
Greece	15 centers	100	2	2	1
Czech Republic	27 ped GIs	100	2	2	0
Israel	61 ped GIs	69	2	2	0
Finland	15 ped GIs	100	2	1	1
Romania	15 ped GIs	100	2	2	0
Italy	35 ped GIs	94	2	1	1
Croatia	10 centers	100	1	0	1
Hungary	10 centers	100	1	0	1
France	27 centers	44	1	0	1
Belgium	11 centers	100	0	0	0
Switzerland	5 centers	60	0	0	0
Portugal	9 centers	100	0	0	0
Denmark	16 centers	56	0	0	0
Austria	14 ped GIs	50	0	0	0

Ped GI, pediatric gastroenterologist; NA, not available.

de Ridder L. Porto IBD Working Group of ESPGHAN. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the porto pediatric IBD group. Inflamm Bowel Dis. **2014** Feb;20(2):291-300.

Kell-e attól félnünk, hogy IBDs gyermekben malignitás alakul ki?

TABLE 3. Reported Pediatric IBD Cases Who Developed Cancer Before the Age of 18 Years, During the Period 2006–2011 (n = 18)

	Age at Diagnosis of IBD (yr)/Sex, Type of IBD	Type of Cancer	Age at Development of Cancer (yr)	Mortality	Immunosuppressants Last 3 mo (Duration)/Other Drugs	Biologicals Last 3 mo (Duration)	Calcineurin Inhibitor Last 3 mo (Duration)
1	3/F, UC	Cholangiocarcinoma	8	No	Thiopurine (18)	No	No
2	2/M, UC	HSTCL	9	No	Steroids, thiopurine (72)	No	No
3	12/F, CD	Acute lymphoid leukemia	13	No	Steroids, thiopurine (12)	No	No
4	8/M, CD	Primitive neuroectodermal tumor	14	Yes	Steroids, thiopurine (12)	No	Yes (9)
5	2/M, IBD-U	HSTCL	15	Yes	Thiopurine (108), sulfasalazine	No	Yes (18)
6	10/M, CD	EBV-associated lymphoma	15	Yes	Steroids, thiopurine (12)	No	Yes (25)
7	15/M, CD	Acute myeloid leukemia	15	No	Thiopurine (10)	No	No
8	14/M, CD	Medulloblastoma	15	No	No	Yes (18)	No
9	10/F, CD	Pilocytic astrocytoma of cerebellum	15	No	Methotrexate (30)	No	No
10	3/M, UC	Adenocarcinoma of colon	16	Yes	Steroids, thiopurine (240)	Yes (24)	Yes (16)
11	15/M, CD	Hodgkin's lymphoma	16	No	Thiopurine (2)	No	No
12	15/M, CD	EBV-positive Hodgkin-like lymphoma	16	No	Thiopurine (21)	No	No
13	12/M, CD	Hodgkin lymphoma	16	No	Thiopurine (48)	No	No
14	9/M, CD	EBV-associated lymphoma	17	No	Thiopurine (96)	Unknown	Unknown
15	14/M, CD	Basal cell carcinoma	17	No	No	Yes (24)	No
16	17/M, CD	Hodgkin lymphoma	17	No	Thiopurine (3)	No	No
17	16/M, CD	Chromophobic renal carcinoma	17	No	Steroids, mesalamine	No	No
18	15/M, CD	HSTCL	18	Yes	Steroids, thiopurine (32)	No	Yes (8)

IBD-U, inflammatory bowel disease unclassified.

de Ridder L. Porto IBD Working Group of ESPGHAN. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the porto pediatric IBD group. Inflamm Bowel Dis. **2014** Feb;20(2):291-300.

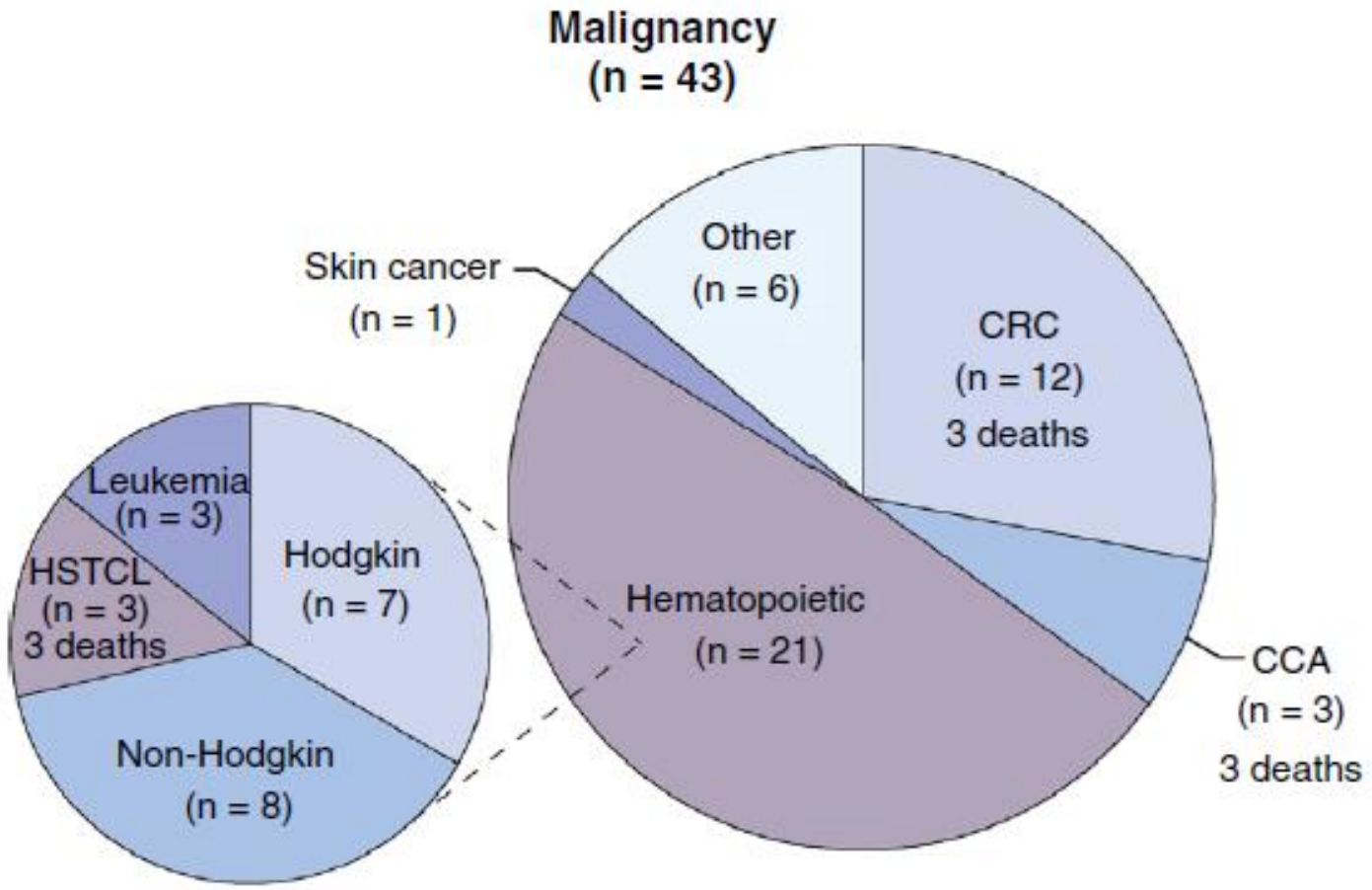
Joosse ME, Paediatric IBD Porto group of ESPGHAN. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. Aliment Pharmacol Ther. 2018 Sep;48(5):523-537.

25 ország, 42 hónap (2013-2016)

PIBD gyermek, akiknél 26 éves koruk előtt malignitást diagnosztizáltak

43-nál rosszindulatú daganat, 9-ben fatális

Joosse ME, Paediatric IBD Porto group of ESPGHAN. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. Aliment Pharmacol Ther. 2018 Sep;48(5):523-537.



Joosse ME, Paediatric IBD Porto group of ESPGHAN. Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. Aliment Pharmacol Ther. 2018 Sep;48(5):523-537.

TABLE 4 Medication exposure in paediatric-onset IBD patients who developed a malignancy

	Total (n = 60)	Hematopoietic (n = 21)	HSTCL (n = 3)	Non-HSTCL (n = 18)	Adenocarcinoma (n = 15)	CRC (n = 12)	CCA (n = 3)	*P* value
Total exposure								
Thiopurines (ever exposed, N (%)	49 (81.6)	20 (95.2)	3 (100)	17 (94.4)	10 (66.6)	9 (75.0)	1 (33.3)	0.063
Biologics (ever exposed), N (%)	22 (36.7)	9 (42.8)	0 (0)	9 (50.0)	5 (33.3)	5 (41.7)	0 (0)	0.732
Methotrexate (ever exposed), N (%)	9 (15.0)	3 (14.2)	0 (0)	3 (16.7)	2 (13.3)	2 (16.7)	0 (0)	1.00
Steroids (ever exposed), N (%)	44 (73.3)	16 (76.2)	3 (100)	13 (72.2)	11 (73.3)	9 (75.0)	2 (66.6)	1.00
Calcineurin inhibitor (ever exposed), N (%)	5 (8.3)	2 (9.5)	0 (0)	2 (11.1)	1 (6.7)	1 (8.3)	0 (0)	1.00
Duration of total exposure								
Duration thiopurine (y, median + IQR)	2.5 (0.9-5.7)[a]	2.6 (0.9-4.8)	4.2 (4.0-5.0)	1.9 (0.9-4.5)	6.0 (1.5-8.6)	6.0 (1.3-8.8)	6.0 (NA)	0.13
Duration biologic (y, median + IQR)	2.2 (0.6-4.0)[a]	3.0 (2.1-4.8)	NA	3.0 (2.1-4.8)	2.0 (0.3-2.5)	2.0 (0.3-2.5)	NA	0.083

Kell-e attól félnünk, hogy IBDs gyermekben malignitás alakul ki?

Összefoglalva:

- Limphoma (HSTCL vagy EBV-pozitív) - vs. kezeléshez kapcsolódtak
- Anti-TNF + AZA veszélyes lehet - bár ebben a csoportban mindenki AZA monoterápián volt
- Gyakori még: Hodgkin-kór (serdülő kori koincidencia?)
- emésztőszervi adenocarcinoma is előfordul

de Ridder L. Porto IBD Working Group of ESPGHAN. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the porto pediatric IBD group. Inflamm Bowel Dis. **2014** Feb;20(2):291-300.

Kell-e attól félnünk, hogy gyermekkorban induló IBD-ben később nagyobb eséllyel alakul ki malignitás?

- a betegség miatt
- az alkalmazott kezelések miatt
  - hatóanyag
  - expozíció ideje

P-IBD – (colorectalis) malignitás kockázat

Study	Location	Setting-design	Follow-up period	Main findings
El-Matary (4)	Canada	Population-based with age, sex and location matched controls reporting any cancer	Persons with IBD and their controls were followed for 14,938 and 132,202 persons-years, respectively	1.7% of childhood-onset IBD developed cancer, as compared with 0.8% of controls HR = 2.00, (95% CI 1.16–3.43), with cancer rates of 114 and 57 per 100,000 person-years, respectively
El-Matary (20)	International (54 centers)	Retrospective hospital-based reporting CRC in children with PSC-UC	Median duration of follow up of 5 years	The incidence of colorectal dysplasia/cancer in pediatric PSC-UC was 2.8 cases per 1,000 person-years
Olen (21, 22)	Scandinavia	Population-based with age, sex, calendar year, and location matched controls reporting CRC in all age groups including pediatric onset IBD	The study period was from 1969 to 2017	CRC deaths in those diagnosed with UC before the age of 18 y to be 34.2 (95% CI 18.8–62.2). The risk was also elevated among those with CD
Olen (23)	Sweden	Cohort [national patient registry (excluding primary outpatient care)] with age, sex, and location matched controls reporting any cancer including CRC in pediatric-onset IBD	148,682 patient-years	HR for any cancer: UC: 2.6 (2.3–3.0) CD: 1.7 (1.5–2.1) HR for CRC UC: 33 (23-49) CD: 5.8 (3.2–10)

El-Matary W, Bernstein CN. Cancer Risk in Pediatric-Onset Inflammatory Bowel Disease. Front Pediatr. 2020 Jul 17;8:400.

P-IBD – (colorectalis) malignitás kockázat

Joosse (24)	European multi-center	Retrospective hospital-based reporting any cancer in pediatric-onset IBD	Estimated 192,625 patient-years	Estimated cancer (any type) incidence of 171 per 1,000,000
Hyams (25)	North American multi-center	Prospective hospital-based reporting any cancer in pediatric-onset IBD	24,543 patient-years. A total follow up period of 9 year	15 cancers, eight of which were lymphoma and leukemia, and five hemophagocytic syndrome. Thiopurine exposed: 2.9 vs. Non-exposed: 1.3
Kappelman (26)	Denmark	Cohort using the Danish health care databases reporting any cancer in pediatric-onset IBD	Not clear	SIR for those with CD 2.3 and 2.0 for UC
Jess (27)	Denmark	Cohort (Nation-wide Cohort) reporting CRC in all age groups including pediatric-onset IBD (<20 y)	178 million person-years of follow-up	The relative risk for developing CRC in pediatric PSC-UC was 44 and 2 for CD CRC did not increase except in those diagnosed with pediatric-onset UC or those with concomitant PSC
Peneau (28)	France	Cohort reporting any cancer in pediatric-onset IBD	Median follow up period of 15 years	Nine cancers including two with CRC SIR = 3.0 (1.3–5.9)
Ekbom (29)	Sweden	Population-based controlled study reporting CRC in pediatric-onset UC	4,220 person-years	SIR of CRC in patients diagnosed with UC (0–14 y) was 118.3 (95% CI 63–202.3)

El-Matary W, Bernstein CN. Cancer Risk in Pediatric-Onset Inflammatory Bowel Disease. Front Pediatr. 2020 Jul 17;8:400.

Eaden JA et al.: The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. **2001** Apr;48(4):526-35.

116 tanulmány metaanalízise

10 év - 2%
20 év - 8%
30 év- 18%

Földrajzi eltérés is mutatkozik:
5/1000 pyd - USA
2/1000 pyd - Skandinavia

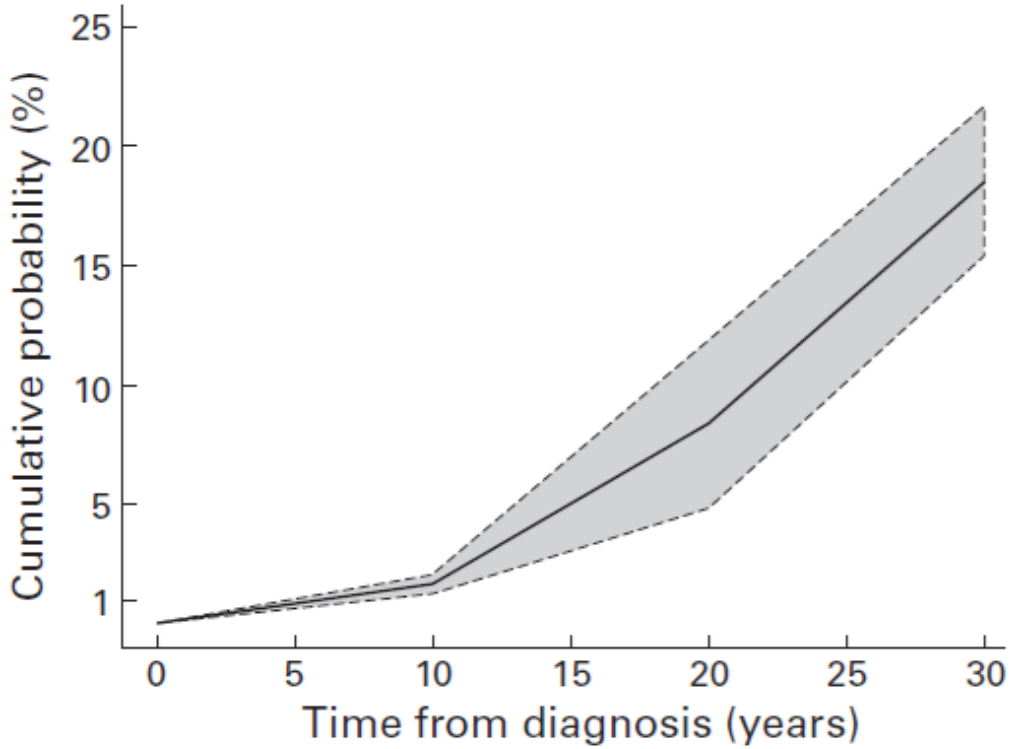


Figure 3 Cumulative risk of developing colorectal cancer for any patient with ulcerative colitis based on stratified data (using stratified incidence, n=19).

Lakatos PL et al: Risk of colorectal cancer and small bowel adenocarcinoma in Crohn's disease: a population-based study from western **Hungary 1977-2008**. J Crohns Colitis. 2011 Apr;5(2):122-8.

506 (5758 betegév) beteg – 5 CRC

Table 2 Clinical characteristics of Crohn's disease-associated colorectal cancer patients.

No	Gender	Smoking	Age at symptom onset (years)	Age at onset of CD (years)	Age at diagnosis of CRC (years)	Duration of CD at diagnosis CRC (years)	CD location at diagnosis	CD behavior at diagnosis	CRC location	Calendar year of diagnosis
1	male	yes	29	30	35	5	coecum-transverse-ascendent	stenosing	transverse colon	1991
2	male	yes	47	47	50	3	coecum-ascendent	stenosing	ascendent colon	2001
3	male	yes	55	56	59	3	terminal ileum-ascendent	stenosing	coecum	2005
4	male	ex	60	61	64	3	terminal ileum	stenosing	coecum	2006
5	male	ex	64	64	66	2	terminal ileum	stenosing	sigmoid colon	2007

Lakatos PL et al: Risk of colorectal cancer and small bowel adenocarcinoma in Crohn's disease: a population-based study from western **Hungary 1977-2008**. J Crohns Colitis. 2011 Apr;5(2):122-8.

Standardized incidence ratio (SIR) nem nagyobb az elvárthoz képest

Férfiakban gyakoribb volt (SIR: 1.95, 95% CI: 0.81–4.70)

Rövid betegséglefolyás után

Függetlenkockázati tényezők

- **Diagnózis kori életkor - idősebbekben**
- Férfi nem
- Sztenotizáló betegség típus

Kummulatív kockázat 20 év alatt 1.1% - nemzetközi adatoknál kedvezőbb

El-Matary W et al.: Long-term Cancer Risk in Patients With **Pediatric-Onset Inflammatory Bowel** Diseases in the **Canadian Population**. Gastroenterology. 2020 Jul;159(1):386-387.

IBD és kontrollcsoport (14,938 és 132,202 betegév)

Átlagéletkor diagnóziskor: 14 év

Átlagéletkor a malignitás diagnózisakor: 37év

Malignitás kockázat 114 vs 57/100.000 fő

Kockázat: **CD: 2.7**, UC: 1.24 (NS)

CRC, NMSC, lymphoma, leukemia, hólyagrák (mind<6eset)

Thiopurin és aTNF nem befolyásolta az előfordulást anti-TNF OR: 0.56

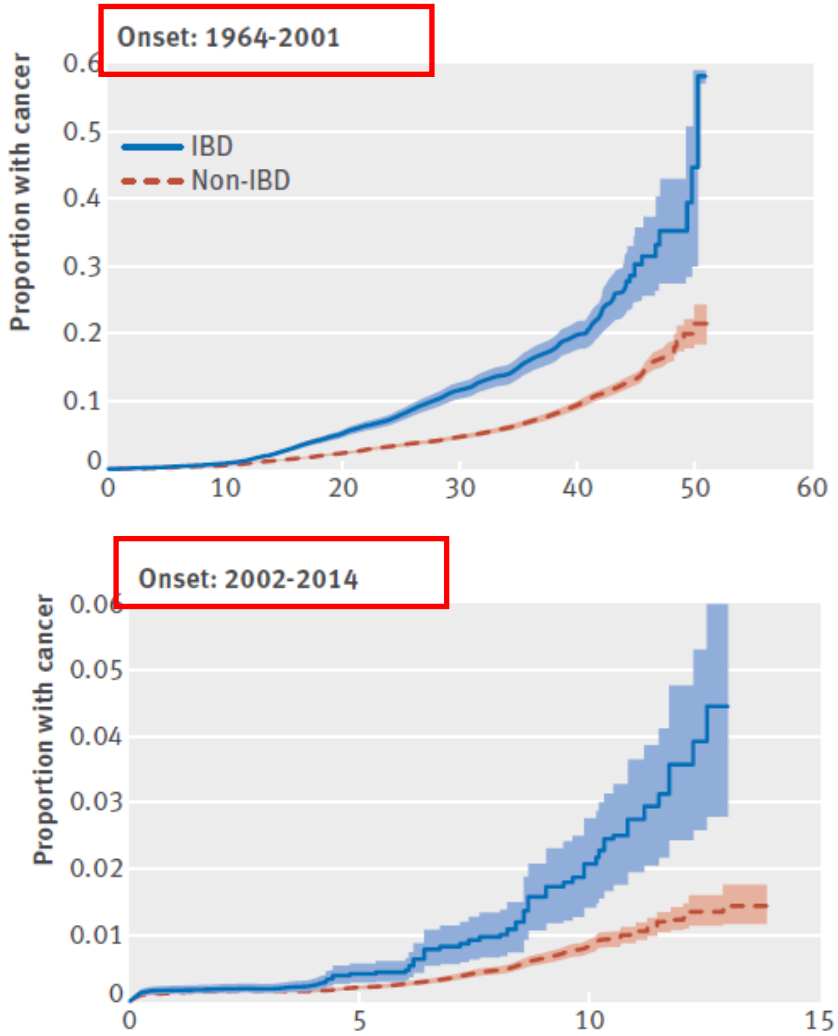
Olén O et al.: **Childhood onset** inflammatory bowel disease and risk of cancer: a Swedish **nationwide cohort study 1964-2014**. BMJ. 2017 Sep 20;358:j3951.

9408 IBD eset,
4648 UC; 3768 CD; 989 IBD-U vs.
92870 kontroll

18 éves kor alatt észlelt IBD-ben malignitás esélye dupla

Malignitásra általában HR:
- UC-ben 2.6,
- CD-ben 1.7

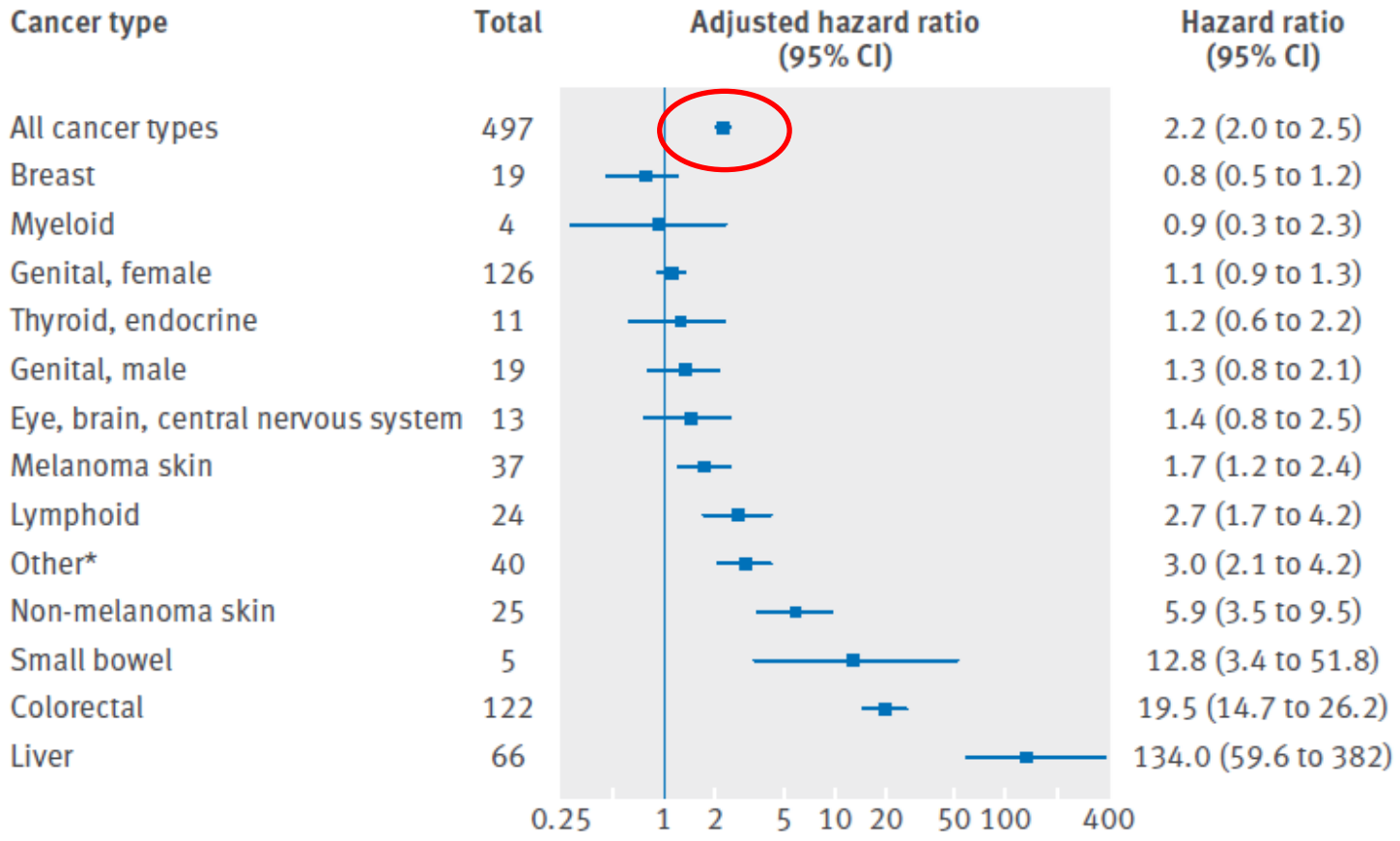
CRC kockázat: UC:33x; CD: 5.8x



Olén O et al.: **Childhood onset** inflammatory bowel disease and risk of cancer: a Swedish **nationwide cohort study 1964-2014**. BMJ. 2017 Sep 20;358:j3951.

PIBD vs. átlagnépességben megjelenő malignitások

GI tumorok HR: 18x!!!



Jess T et al.: Decreasing risk of **colorectal cancer** in patients with inflammatory bowel **disease over 30 years**. Gastroenterology. 2012 Aug;143(2):375-81.

178 millió betegév elemzése
268 UC és 70 CD betegnél CRC

UC-ben CRC kockázat az átlagpopulációéhoz mérhető (1.07), de **fokozott**

- **gyermekkori diagnózis,**
- **hosszú lefolyás**
- **PSC társulása**

1979-1988 között CRC RR : 1.34 0.57 (95% CI, 0.41-0.80)
1999-2008 között: 0.57.

CD-ben 0.85, nem változott az elmúlt évtizedekben

Kell-e félnünk a malignitástól PIBD-ből átvett betegeinknél?

Table 1 | Childhood onset inflammatory bowel disease and risk of cancer

Study	Study period	Age at onset, years	No of patients followed (sub-type)	Patient years of follow-up	Number of cancers diagnosed	Incidence per 1000 person years (95% CI)	Relative risk*
Devroede, 1971	USA 1919-65	<14	396 (UC)	NR, max 43 years	52 (any cancer)	NR	NA
Weedon,1973	USA 1919-65	<22 (mean 15)	449 (CD)	7077	12 (any cancer) 8 (CRC)	1.0 (0.5 to 2.1) for CRC	20 for CRC
Goel, 1973	Scotland 1931-71	<14 (mean 8)	25 (UC)	303	1 (CRC)	3.3 (0.2 to 16.3)	NR
Ekbom, 1990	Sweden 1945-83	<15	363 (UC)	4220	13 (CRC)	3.1 (1.7 to 16.3)	118 (63 to 202)
Ekbom, 1990	Sweden 1983-84	<30	964 (CD)	12 025	5 (CRC)	0.4 (0.2 to 0.9)	10 (3 to 23)
Ashworth, 2012						to 1.5)	8 (0.7 to 42)
Jess, 2012						to 0.5)	UC: 44 (27 to 719) CD: 2 (0.3 to 17)
Peneau, 2013							3.0 (1.3 to 5.9)
de Ridder, 2014							NA
Kappelman, 2014							UC: 2.0 (1.4 to 2.7) CD: 2.3 (1.5 to 3.4)
Hyams, 2017	USA, Europe 2007-16	<17	5766 (UC,CD)	24 543	15 (any cancer) 9 (lymphoid)	0.6 (0.4 to 1.0)†	Thio exposed: 2.9 (1.4 to 5.1) Non-exposed: 1.3 (0.2 to 4.7)
Current study	Sweden 1964-2014	<18 (median 15)	9405 (UC,CD)	148 682	497 (any cancer) 122 (CRC) 24 (lymphoid)	3.3 (3.1 to 3.6)‡ 0.6 (0.4 to 0.9)§	HR for any cancer: UC: 2.6 (2.3 to 3.0) CD: 1.7 (1.5 to 2.1) HR for CRC UC: 33 (23 to 49) CD: 5.8 (3.2 to 10)

CD=Crohn's disease; CI=confidence interval; CRC=colorectal cancer; HR=Hazard Ratio; NA=Not applicable; NR=not reported; thio=thiopurines; UC=ulcerative colitis.
*Standardised incidence ratio, unless otherwise stated
†Followed up until 23rd birthday
‡All follow-up
§Followed up until 18th birthday

Magánvélemény:
Jobb félni, mint megijedni!!

CD: 20x

UC: 118x
CD: 10x
IBD: 8x
IBD3x

IBD~2x

AZA+:1.4-5.1
AZA-: 0.2-4.7

Olén O et al.: Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014. BMJ. 2017 Sep 20;358:j3951.

Kell-e félnünk a malignitástól PIBD-ből átvett betegeinknél?

Statement 1

Patients with IBD of the colon should be informed that they are at increased risk of developing colorectal cancer [CRC] [EL1]

The risk of colorectal cancer is highest in patients with ulcerative colitis [UC] with extensive disease, and increases significantly 8–10 years after diagnosis or when dysplasia is detected on colonic biopsies [or both], particularly high-grade dysplasia [EL1]

Risk factors include male sex, young age at UC diagnosis, family history of CRC, and the presence of colonic strictures or primary sclerosing cholangitis [EL1] **Consensus: 100%**

Kell-e félnünk a malignitástól PIBD-ből átvett betegeinknél?

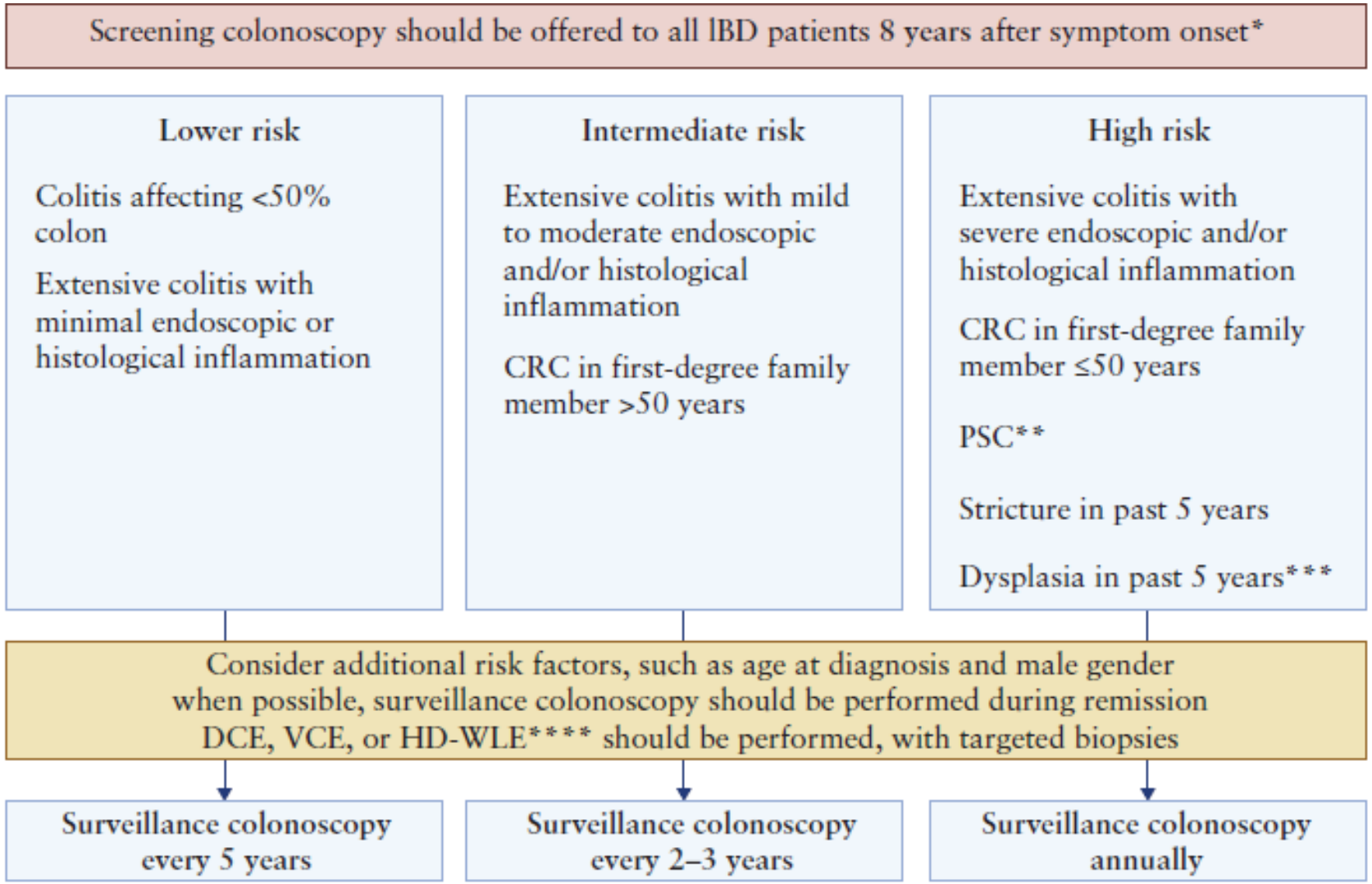
Statement 6

Patients with IBD are at higher risk for cholangiocarcinoma compared with the general population, particularly patients with UC and concomitant PSC [EL3]

Surveillance for cholangiocarcinoma should be considered in all patients with IBD and PSC regardless of disease stage, and is most relevant in the first year after diagnosis [EL3]

Surveillance for cholangiocarcinoma should include appropriate imaging and should be performed every 6 to 12 months [EL4] **Consensus: 100%**

CRC – egyértelmű szűrési javaslat



Kell-e szűrni a vékonybél daganatokra?

Statement 7

Patients with CD, particularly those with small-bowel involvement, have an increased risk of small-bowel cancers [EL1]

Small-bowel adenocarcinoma is the most common subtype and is found in areas of inflammation, predominantly the distal jejunum and ileum. [EL3] The diagnosis should be considered in patients with refractory, long-standing, stricturing disease or relevant symptoms [EL5]

At present, routine surveillance with imaging or endoscopy is not recommended for small-bowel cancers [EL5]

Consensus: 95.0%

Kell-e szűrni az extraintesztinális tumorokra?

Statement 8

There is a small increased risk of non-gastrointestinal solid-organ tumours in IBD compared with the general population. [EL2] Since there is no evidence to recommend a different approach to prevention and early diagnoses of extraintestinal cancers, patients with IBD should be encouraged to follow the same primary and secondary prevention programmes as the general population, based on individual risks [EL5] **Consensus: 100%**

Kell-e tartanunk a gyógyszeres kezelésektől?

Table 2. Cancer risk associated with conventional and advanced IBD therapies

Drug	Cancer	Evidence level	Additional considerations
Thiopurine	Lymphoproliferative	EL1	EBV exposure
	Myeloproliferative	EL3	Age
	NMSC	EL2	Gender
	Cervical	EL4	Cervical cancer risk not replicated in all cohorts
TNF antagonist	Lymphoma	EL2	Risk not replicated in all cohorts
	Melanoma	EL2	
TNF antagonist with thiopurine	Lymphoma	EL2	Risk increased compared with both unexposed populations and monotherapy
Vedolizumab	None	EL4	Limited duration of follow-up
Ustekinumab	None	EL4	Limited duration of follow-up in IBD; data from non-IBD indications with lower doses
JAK inhibitors	All except NMSC	EL4	In high-risk RA population only Not replicated in IBD
Methotrexate	NMSC	EL5	Risk not replicated NMSC in all cohorts

Kell-e attól félnünk, hogy gyermekkorban induló IBD-ben később nagyobb eséllyel alakul ki malignitás?

- a betegség miatt – idővel biztos, a mérték bizonytalan
- az alkalmazott kezelések miatt
  - hatóanyag – thiopuron, aTNF
  - expozíció ideje – minden bizonnyal

Összefoglalás

Ti szűrtök-e CRC-re 5 éves korban induló pancolitises betegnél 13 éves kortól, vagy PSC esetén a diagnózistól évente ?

Csináltok-e EBV szerológiát az immunszupresszioó indítása előtt? Befolyásolja-e a terápiás stratégiát az eredmény (mono vs. kombo)?

Van-e nálatok checkpoint inhibitor szövődményeként kialakult colitis, és mit csináltok vele?

Köszönöm a figyelmet!

SEMMELWEIS
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