Does My Treatment Cause Cancer?

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November 6, 2020

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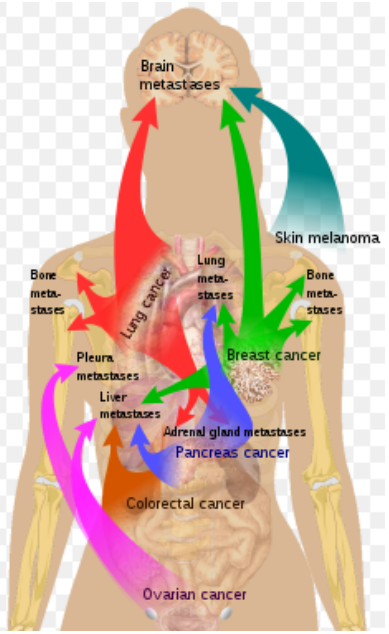
Disclosures

- AbbVie- Consultant
- UCB –Consultant
- Pfizer- Consultant, Grant support
- Takeda- Consultant, Grant support
- Janssen- Consultant
- Target PharmaSolutions – Consultant
- Prometheus- Consultant
- Salix – Consultant
- Valeant – Consultant
- Genetech/Roche – Consultant

Outline: IBD and Cancer

- Epidemiology of malignancy in IBD
- Risks of malignancy associated with therapies
  - Have the new biologics changed the landscape?
- Recurrence of malignancy
  - If you have cancer, what treatment?
  - Example case
- Risk communication with patients on malignancy
- Role of prevention of malignancy in IBD



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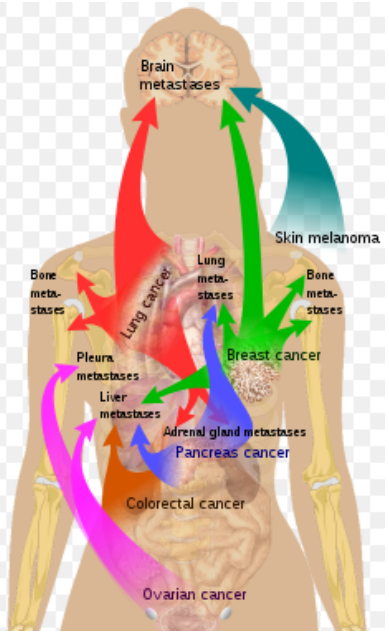
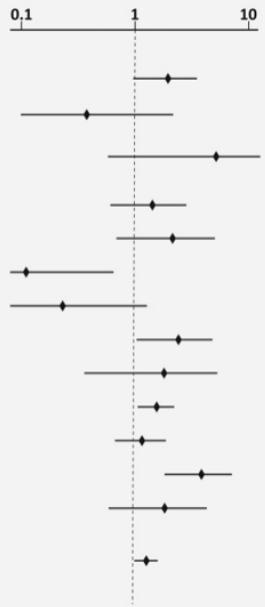


Epidemiology: Cancer Risk in IBD: Dutch IBDSL cohort

- 79 primary cancers were observed in 73 CD patients, overall cancer risk (SIR 1.28; 95% CI 1.01–1.60)
- Increase was associated with:
  - Male gender (SIR 1.41; 95% CI 1.01–1.93)
  - >40 years of age at CD diagnosis (SIR 1.36; 95% CI 1.05–1.73)
  - Ileal localization at CD diagnosis (SIR 1.38; 95% CI 1.02–1.84)
  - First decade after CD diagnosis (SIR 1.54; 95% CI 1.19–1.97)
  - CD diagnosis in the 2001–2011 era (SIR 1.57; 95% CI 1.08–2.19)

Cancer risks in CD population (n=1157)

Cancer type	O	E	SIR	(95%CI)
CRC	11	5.65	1.95	(0.97-3.48)
Upper GI-tract	1	2.58	0.39	(0.01-2.16)
Liver and bile ducts	2	0.39	5.16	(0.58-18.64)
Lung	8	5.62	1.42	(0.61-2.80)
Urinary tract	5	2.34	2.14	(0.69-5.00)
Breast	1	8.72	**0.11**	**(0.00-0.64)**
Prostate	1	4.43	0.23	(0.00-1.26)
Hematologic	8	3.31	**2.41**	**(1.04-4.76)**
NHL	3	1.67	1.80	(0.36-5.25)
Skin	32	20.59	**1.55**	**(1.06-2.19)**
BCC	17	14.75	1.15	(0.67-1.85)
SCC	10	2.61	**3.83**	**(1.83-7.04)**
Melanoma	5	2.75	1.82	(0.59-4.24)
Overall	79	61.64	**1.28**	**(1.01-1.60)**



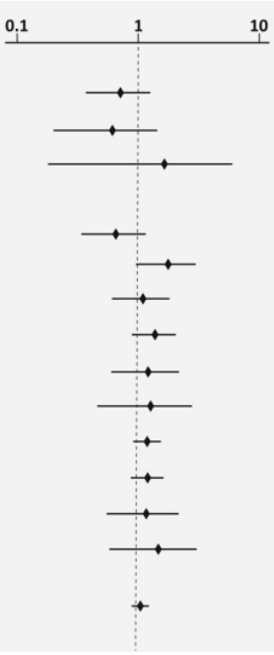
Van den Heuvel TR, et al. Int J Cancer. 2016 Sep 15;139(6):1270-80.

Epidemiology: Cancer Risk in IBD: Dutch IBDSL cohort

- In the total UC population, 172 primary cancers were observed in 158 UC patients
- Overall cancer risk was similar to the background population (SIR 1.03; 95% CI 0.88–1.20)
- Overall cancer risk was increased in the second decade after UC diagnosis (SIR 1.39; 95% CI 1.10–1.73)

Cancer risks in UC population (n=1644)

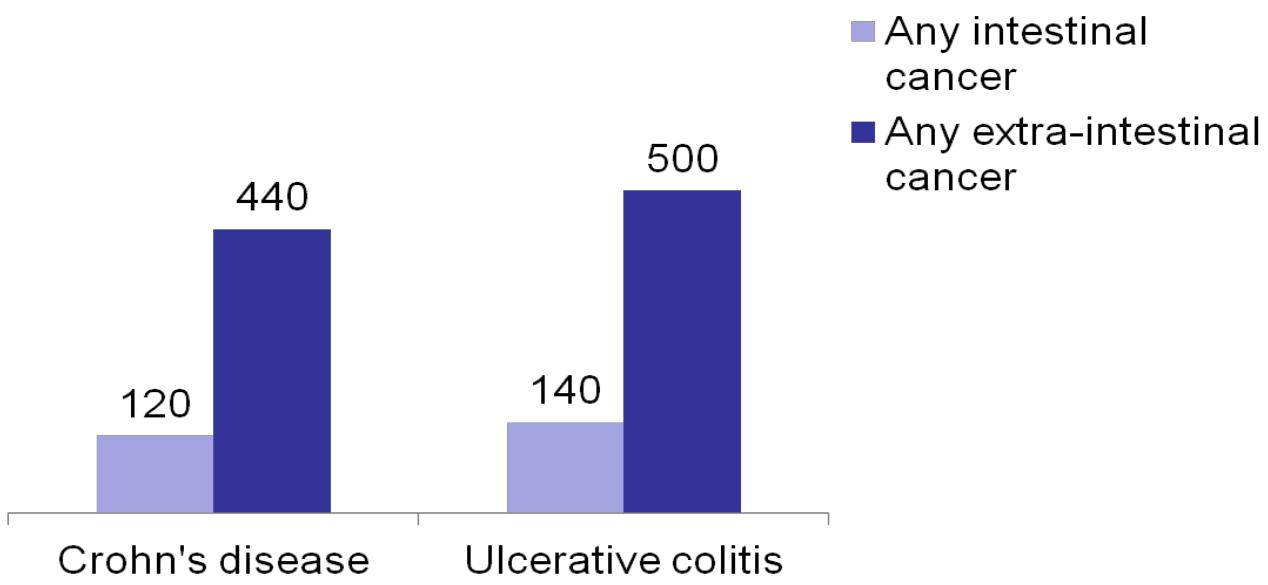
Cancer type	O	E	SIR	(95%CI)
CRC	12	16.84	0.71	(0.37-1.24)
Upper GI-tract	5	8.20	0.61	(0.20-1.42)
Liver and bile ducts	2	1.22	1.64	(0.18-5.92)
Lung	12	18.35	0.65	(0.34-1.14)
Urinary tract	14	7.95	1.76	(0.96-2.95)
Breast	15	13.79	1.09	(0.61-1.79)
Prostate	25	18.26	1.37	(0.89-2.02)
Hematologic	11	9.20	1.20	(0.60-2.14)
NHL	6	4.77	1.26	(0.46-2.74)
Skin	61	51.50	1.18	(0.91-1.52)
BCC	44	36.93	1.19	(0.87-1.60)
SCC	10	8.64	1.16	(0.55-2.13)
Melanoma	7	4.80	1.46	(0.58-3.00)
Overall	172	166.61	1.03	(0.88-1.20)



Van den Heuvel TR, et al. Int J Cancer. 2016 Sep 15;139(6):1270-80.

Cancer in IBD

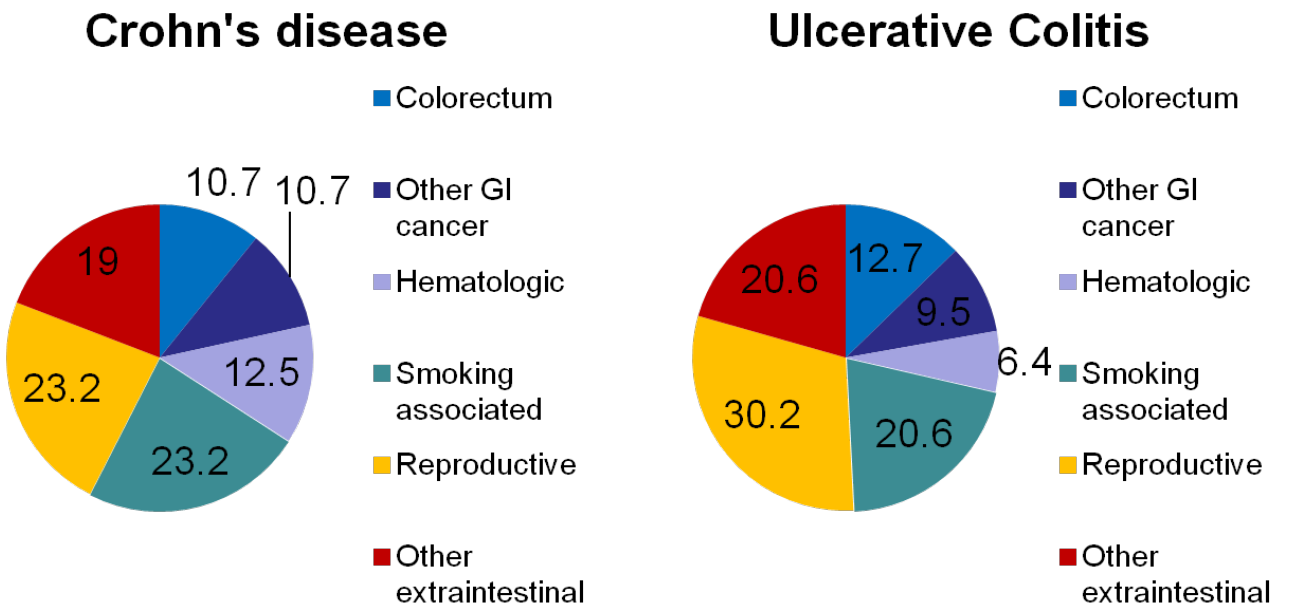
Absolute risk of any malignancy per 10,000 by CD or UC, occurring 1-11 years after IBD diagnosis, Denmark 1978-2010



Kappelman MD, et al. Clin Gastroenterol Hepatol. 2014 Feb;12(2):265-73.

Cancer in IBD

Breakdown by site of cancers occurring 1-11 years following IBD diagnosis, Denmark 1978-2010



Relative risk of extraintestinal cancers among patients with IBD was stable over time, although the risk of GI cancers decreased.

Kappelman MD, et al. Clin Gastroenterol Hepatol. 2014 Feb;12(2):265-73.

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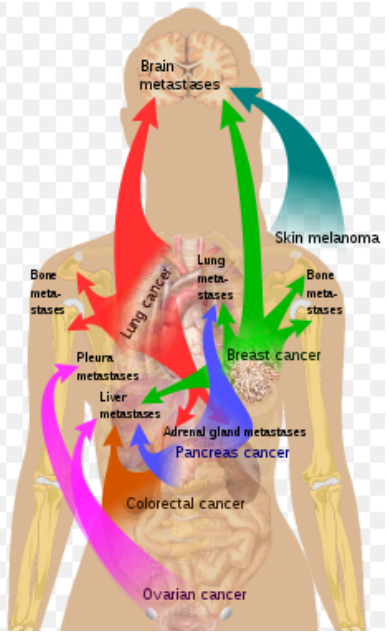
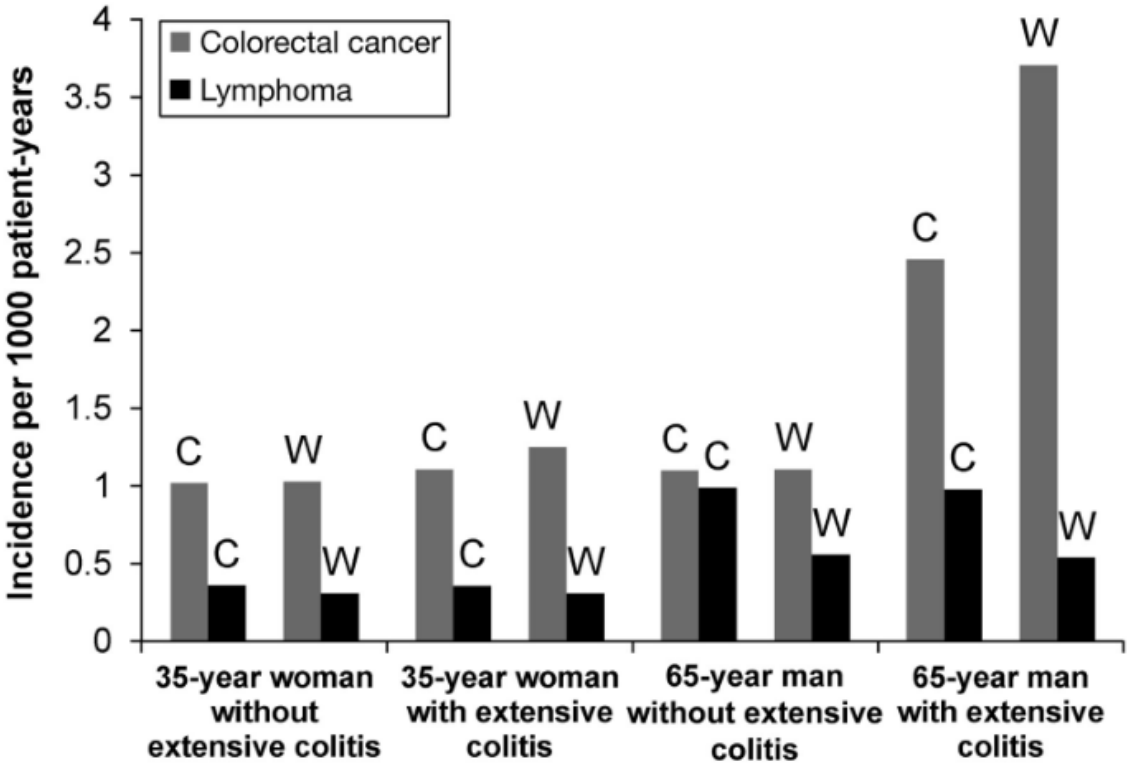


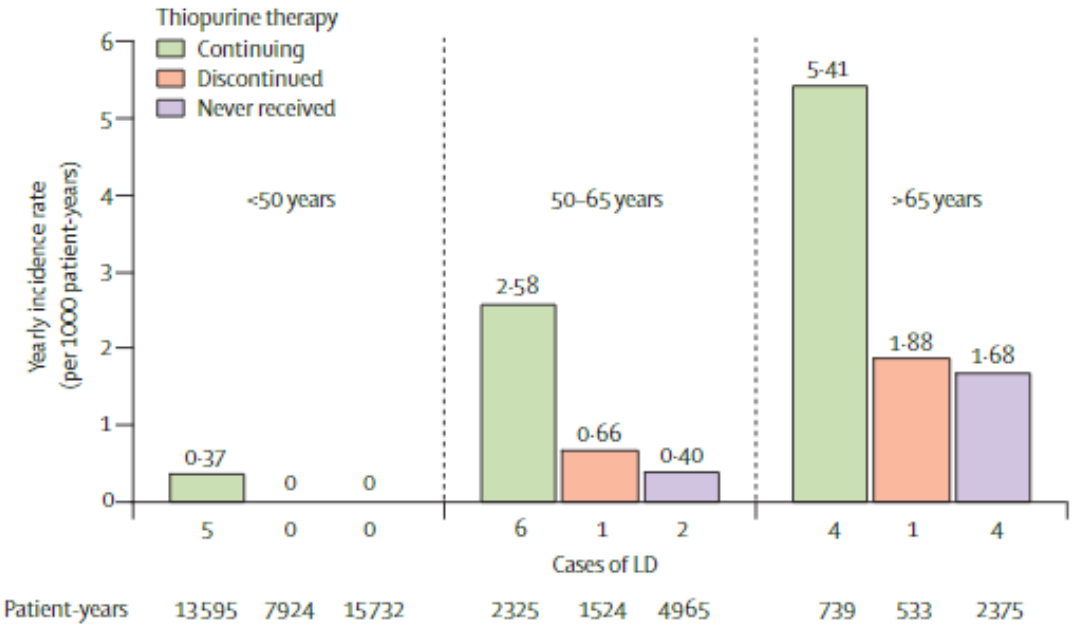
Malignancy Risk in IBD: Relative Risks and Benefits



Lifetime absolute risks of lymphoma and CRC with continuing (C) or withdrawing (W) maintenance therapy with thiopurines

Beaugerie L, et al. *Clin Gastroenterol Hepatol*. 2019 Feb;17(3):370-379.

Lymphoma Incidence w/ Thiopurines and Types of Lymphoma in IBD



Types of Lymphoma in IBD from Systematic Review
Non-Hodgkin's lymphoma (83.9%)
• Diffuse Large B cell (30%)
• Follicular (13%)
Large proportion PIL [22-75%]
Large proportion EBV + [44-75%]

Beaugerie L, et al. Lancet 2009;374:1617-25.
Muller M, et al. J Crohns Colitis 2020. [epub]

Lymphoma Risk with IBD Therapies: Nationwide French National Health Insurance Database

- Patients age 18 and up
- Time period 2009-2013
- 189,289 IBD patients included
- Median follow up of 6.7 years
- Determined classes of exposure:
  - No exposure
  - Thiopurine monotherapy
  - Anti-TNF monotherapy
  - Combination therapy

Group of Exposure as compared to unexposed	Adjusted Hazard Ratio (95% CI)
Thiopurine monotherapy	2.60 (95% CI 1.96-3.44)
Anti-TNF monotherapy	2.41 (95% CI 1.60-3.64)
Combination therapy	6.11 (95% CI 3.46-10.8)

- IR per 1000 p-y unexposed: 0.26 (95% CI 0.23-0.29)
- IR per 1000 p-y thiopurine 0.55 (95% CI 0.41-0.67)
- IR per 1000 p-y anti-TNF 0.41 (95% CI 0.27-0.55)
- IR per 1000 p-y combination 0.95 (95% CI 0.45-1.45)

Lemaitre M, et al. Jama 2017;318:1679-1686.

Hepatosplenic T-cell Lymphoma

Very rare aggressive extranodal form of NHL

- Approximately 40 cases reported cases in IBD

Rapidly fatal lymphoproliferation

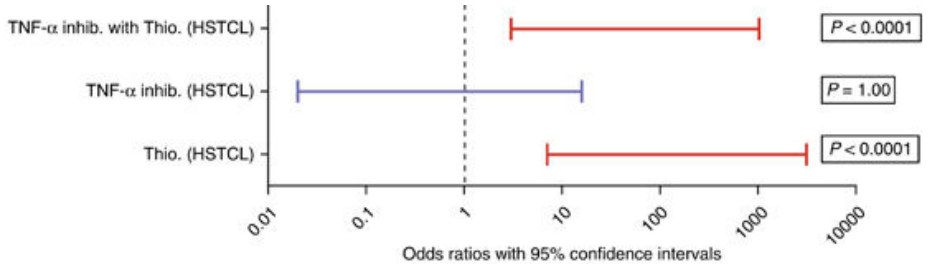
- Mean time from diagnosis to death < 16 months

Does occur de-novo in general population

- Only 10% related to IBD treatment

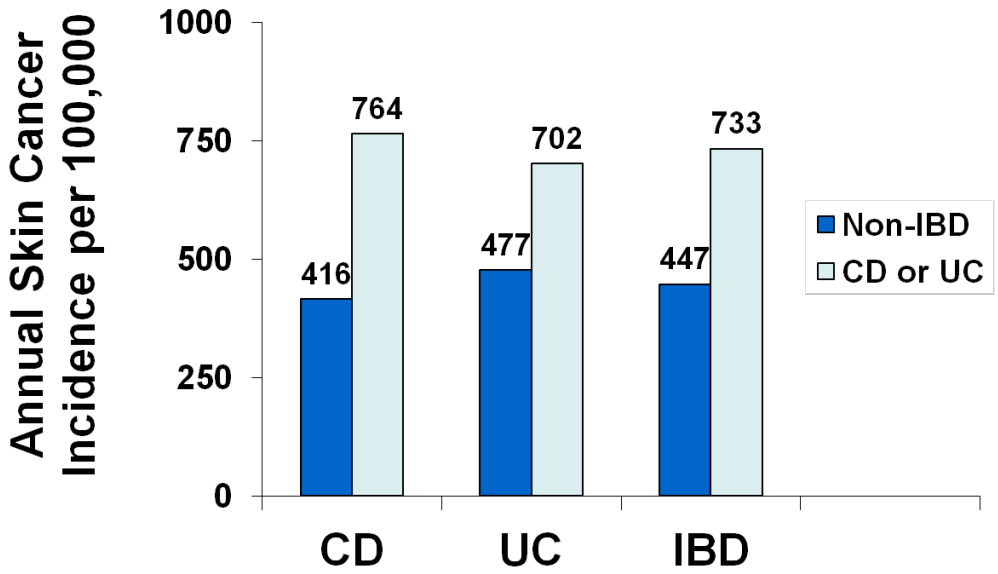
Predominant characteristics in IBD

- Young males (median age 22.5)
- Combination therapy with anti-TNF/thiopurines



Thai A, et al. J Crohns Colitis. 2010 Nov;4(5):511-22.
Kotlyar DS, et al. Clin Gastroenterol Hepatol. 2011 Jan;9(1):36-41.e1.
Deepak P, et al. Am J Gastroenterol. 2013 Jan;108(1):99-105.

Incidence and Medication Risk Factors for NMSC in IBD



Medication *	Crohn's disease	Ulcerative colitis
Thiopurines	OR 4.25 (2.81-6.42)	OR 4.34 (2.53-7.43)
Biologic Anti-TNF	OR 2.18 (1.07-4.46)	N/A
Methotrexate	OR 2.69 (0.63-11.56)	N/A

Medication*	Cases n=228	Controls n=913	OR (95% CI)
None	154 (68%)	817 (89%)	1.0 (reference)
Thiopurine	56 (25%)	73 (8%)	4.45 (2.94-6.75)
Biologic Anti-TNF	7 (3%)	13 (1%)	3.23 (1.24-8.45)
Combination	11 (5%)	10 (1%)	6.75 (2.74-16.65)

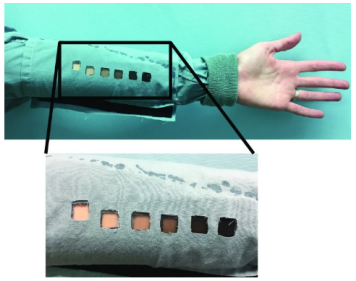
*Persistent medication use, > 1 year

Long MD, et al. Clin Gastro Hepatol. 2010;8:268–274

Mechanism of Thiopurines and NMSC

Azathioprine has been shown to selectively increase photosensitization of human skin to UVA light

– Minimal erythema dose (the lowest amount of radiation required to produce perceptible erythema 24 hours after skin irradiation) shows increased sensitivity to UV-A light



MED Testing

Photo credit:
Conant et al, Dermatol Ther (Heidelb). 2018 Sep;8(3):483-489

Sunlight induces chronic oxidative stress and increases the levels of oxidative DNA skin lesions

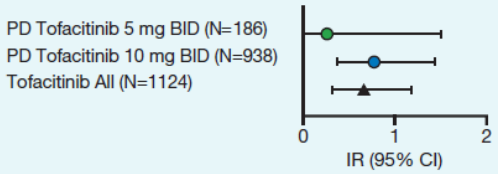
– 6-Thioguanine DNA photoproducts

O'Donovan et al. Science 2005; 309: 1871-4.
Long MD, et al. Inflamm Bowel Dis. 2016 Jan;22(1):E2-3.

Tofacitinib and NMSC

- Data from rheum development program of tofacitinib demonstrate IR of 0.55 per 100 pt-yrs (550/100,000 patient years)
- Data from UC development program of tofacitinib show similar estimates
- Higher doses associated with higher incidence rates

Figure 2. Proportions and IRs[a] of all NMSC events in the Overall Cohort, for PD tofacitinib 5 mg BID, PD tofacitinib 10 mg BID, and for the 'Tofacitinib All' group



	n (%)	Exposure, PY	IR (95% CI)
PD Tofacitinib 5 mg BID (N=186)	1 (0.5)	368.6	0.27 (0.01, 1.51)
PD Tofacitinib 10 mg BID (N=938)	10 (1.1)	1279.2	0.78 (0.37, 1.44)
Tofacitinib All (N=1124)	11 (1.0)	1647.8	0.67 (0.33, 1.19)

[a]Patients with events per 100 PY
BID, twice daily; CI, confidence interval; IR, incidence rate; N, number of patients randomized, treated, and evaluated for adjudicated NMSC; n, number of patients with NMSC; NMSC, non-melanoma skin cancer; PD, predominant dose; PY, patient-years

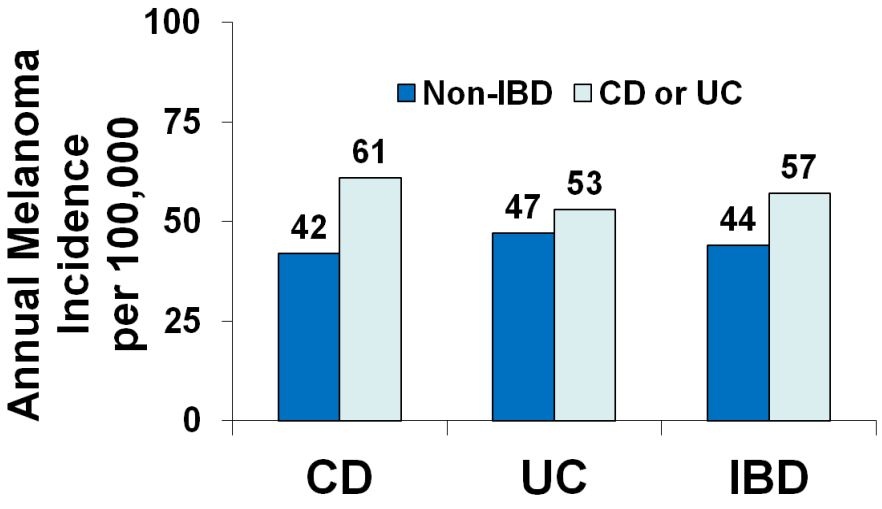
Curtis JR, et al. Clin Exp Rheumatol. 2017 Jul-Aug;35(4):614-622.
Sands BE, Long MD, et al. Am J Gastro 2018; ACG 2018 supplement

Other Biologics and NMSC

- No increased risk of NMSC as compared to placebo in initial RCTs for vedolizumab or ustekinumab
  - Rare cases of NMSC had prior exposure to azathioprine, anti-TNF agents
- PSOLAR registry of biologics and DMARDs for psoriasis (n=12,090, 48,870 p-y)
- Of 6,782 patients with mean 18 year history of psoriasis and no prior NMSC (n=2623 ustekinumab, n=3727 anti-TNF and n=432 MTX)
  - Crude incidence NMSC on a biologic 0.33/100 p-y, on MTX 1.41/100 p-y
  - Risk of developing on-treatment NMSC for ustekinumab lower than that of patients on MTX (incidence 0.19/100 p-y for ustekinumab), (incidence 0.43/100 p-y for anti-TNF)

Srivastava B, et al. EADV Congress 2017
DeShazo R, et al. J Drugs Dermatol. 2019 Oct 1;18(10):1059-1060

Incidence and Medication Risk Factors for Melanoma in IBD



	CD	UC	IBD
IRR	1.45	1.13	1.29
95% CI	1.13-1.85	0.89-1.42	1.09-1.53

Medication*	IBD overall	Crohn's disease	Ulcerative colitis
5ASA	1.06 (0.77-1.45)	0.98 (0.63-1.53)	1.22 (0.76-1.96)
Anti-TNF	1.88 (1.08-3.29)	1.94 (1.03-3.68)	1.73 (0.53-5.63)
Thiopurine	1.10 (0.72-1.67)	0.92 (0.53-1.59)	1.31 (0.66-2.60)

Meta-analysis (12 studies)

- IBD with increased risk (RR 1.37; 95% CI, 1.10-1.70
- Highest risk with CD (RR 1.80; 95% CI, 1.17-2.75)

Long MD, et al. Gastroenterology. 2012 Aug;143(2):390-399.
Singh S, et al. Clin Gastroenterol Hepatol. 2014 Feb;12(2):210-8.

Malignancy and IBD Therapy

	Steroids	Thiopurines	Methotrexate	Anti-TNF	JAK	Anti-integrin	IL 12/23
Lymphoma	No?	↑↑	↑	↑	?	No	No
Non-melanoma skin cancer	Basal cell?	↑↑	↑	↑?	↑↑	No	No
Melanoma	No	No	No	↑	No	No	No
Urinary tract cancer	No	↑?	No	No	No	No	No
Colorectal cancer	No	No or ↓**	No	No or ↓**?	No	No	No
Breast cancer	No	No	No	No	No	No	No
Overall risk of cancer	No	↑	No	↑?	↑?	No	No

**Colorectal cancers associated with inflammation

Adapted from Beaugerie L & Itzkowitz S, N Eng J Med 2015; 372: 1441-52

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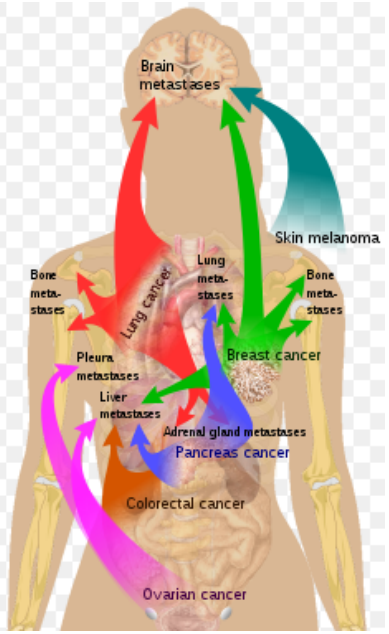


Lessons Learned from Transplant Populations: Cancer Recurrence

- Rates of cancer recurrence in patients with prior cancer and organ transplant are >20% in years following renal transplant
- Rates differ by type of malignancy
- Rates highest when transplantation occurs within 2 years of cancer treatment
  - 54% (1-2 years)
  - 33% (2-5 years)
  - 13% (more than 5 years)

Low <10%	Intermediate (11-25%)	High (>25%)
Incidental renal tumor	**Prostate**	**NMSC**
Lymphoma	**Breast**	**Myeloma**
Testicle	**Wilms**	**Symptomatic renal carcinomas**
Uterus/ cervix	**Bladder**	
Thyroid	**Sarcoma**	
Colon	**Melanoma**	

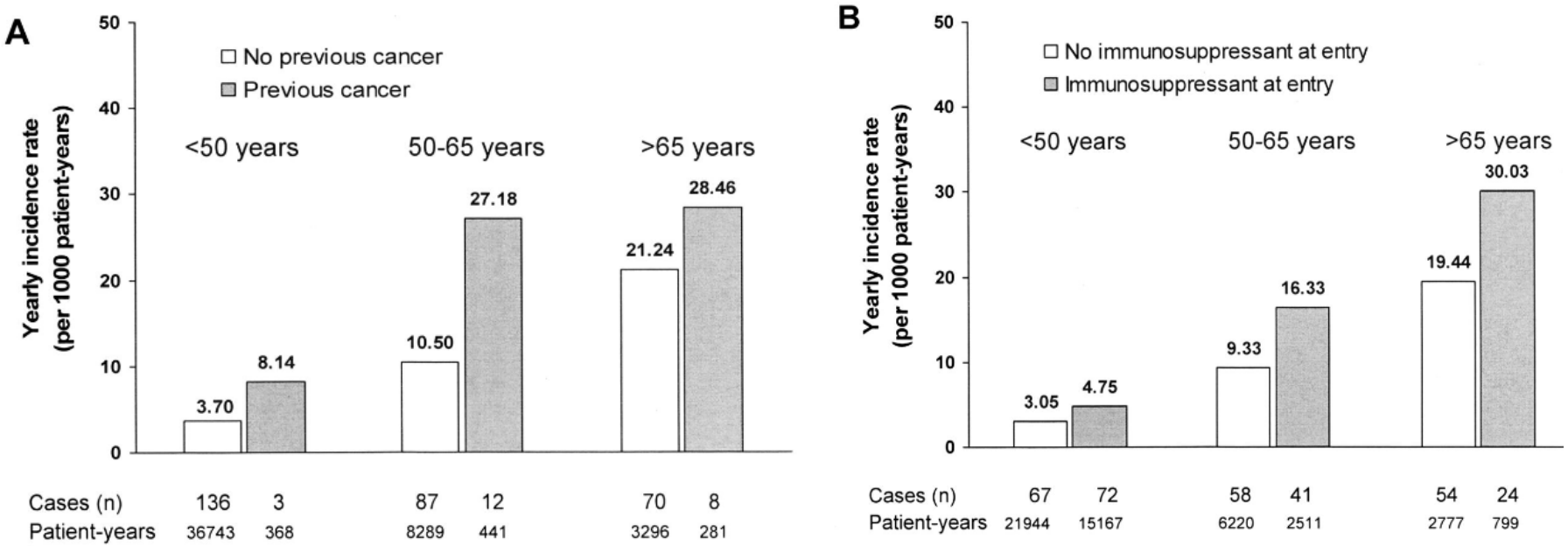
Penn I, Evaluation of transplant candidates with pre-existing malignancies. Ann Transplant 1997;**2**:14–7

IBD Immunosuppression and Cancer Recurrence: Meta-analysis

- 11,707 persons, 31,258 p-y of follow up after a prior diagnosis of cancer
- Recurrence on anti-TNF 33.8 per 1000 p-y
- Recurrence on immunomodulator 36.2 per 1000 p-y
- No immnosupression 37.5 per 1000 p-y
- Numerically higher for combination therapy 54.5 per 1000 p-y, but not significant
- Similar rates for new or primary cancers, and when immunosuppression initiated within 6 years
- Concerns surrounding selection bias, lack of data on early re-initiation of therapy

Shelton E, et al. *Gastroenterology.* 2016 Jul;151(1):97-109

Prospective CESAME IBD Cohort: Risk of New or Recurrent Cancer

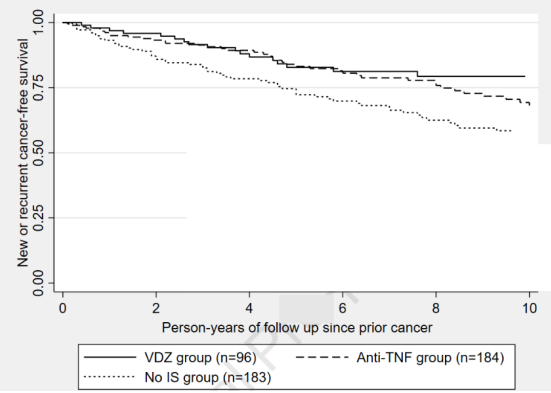


Beaugerie L, et al. Gut 2014;63:1416-23.

Vedlizumab or Anti-TNF and Risk of New or Recurrent Cancer in Patients with IBD with Prior Malignancy

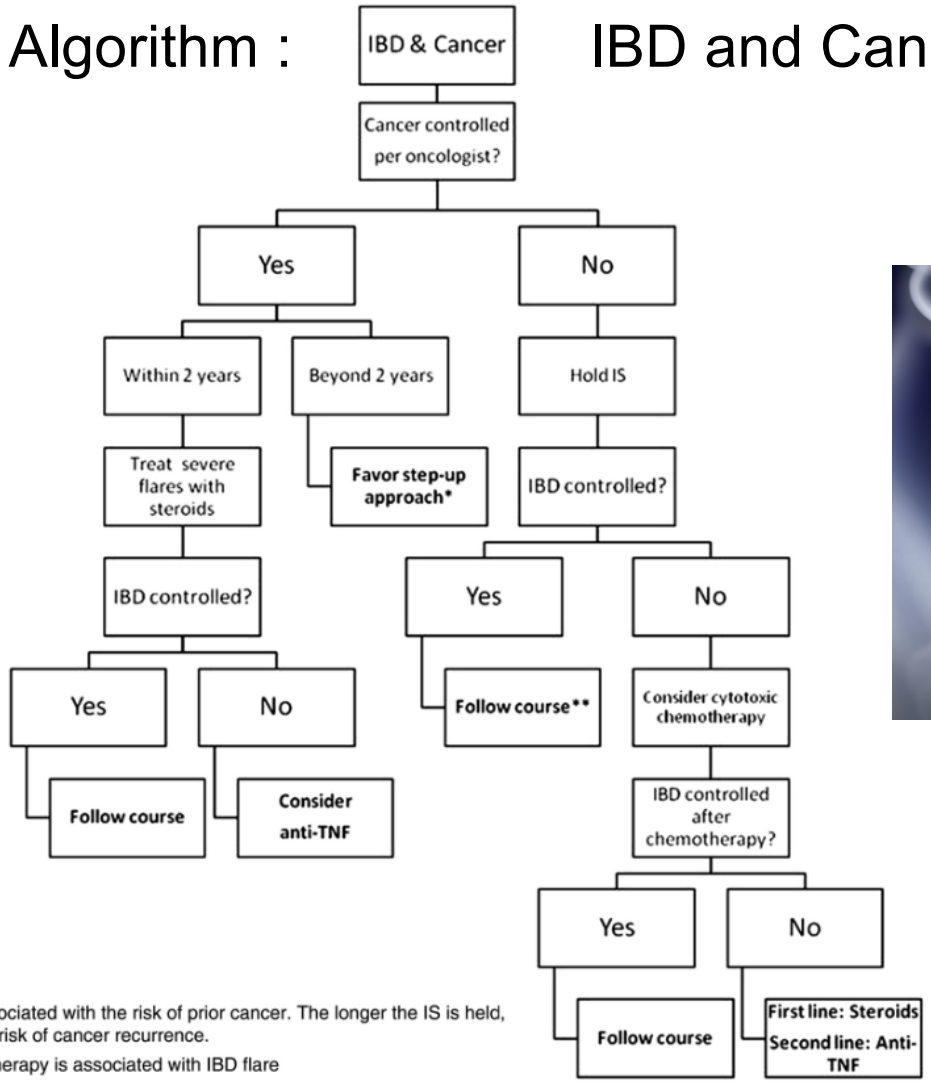
Group (n=463)	No of new or recurrent	Person years of follow up post cancer	Adjusted HR* (95% CI) incident cancer	Adjusted HR* (95% CI) incident cancer (no NMSC)
No immunosuppression	78 (30N/48R)	1378	1.0 (referent)	1.0 (referent)
Vedolizumab	18 (7N/11R)	821	0.72 (0.38-1.39)	0.56 (0.23-1.39)
Anti-TNF	61 (27N/34R)	1452	1.03 (0.65-1.64)	0.87 (0.45-1.65)

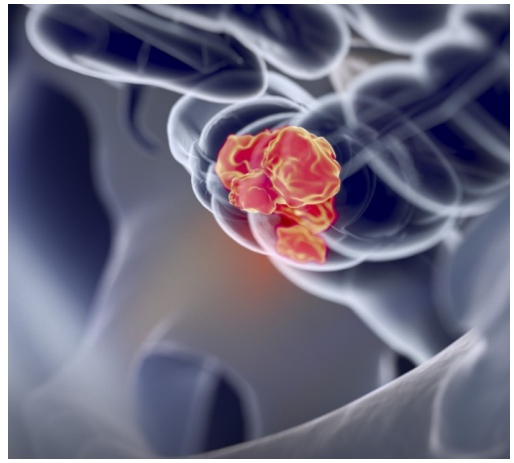
*adjusted for age, IBD subtype, smoking, antimetabolite exposure, cancer category, cancer stage, and time to biologic



Vedamurthy, A et al. Clin Gastroenterol Hepatol 2020. [epub]

Proposed Algorithm : IBD and Cancer Recurrence





*Avoid IS associated with the risk of prior cancer. The longer the IS is held, the lower the risk of cancer recurrence.

**Hormonal therapy is associated with IBD flare

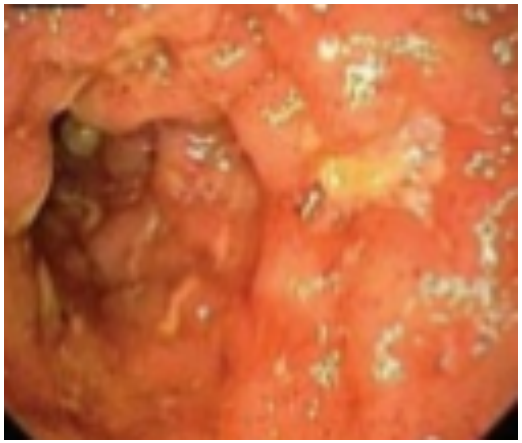
Bernheim O, et al. Gut. 2013 Nov;62(11):1523-8.

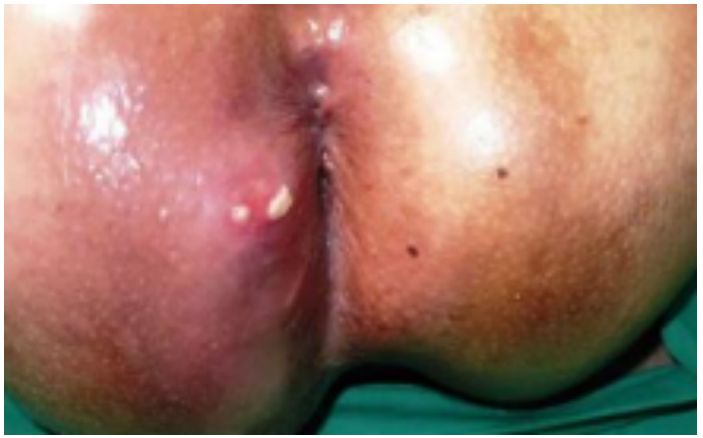
Case

- 48 year old woman with Crohn's disease, ileocolonic (predominantly rectal and ileal), with perianal phenotype
  - Prior ileal resection
  - Maintained on adalimumab post-op with endoscopic remission
- Diagnosed with breast cancer, 3 locally invasive ductal tumors (small in size), lumpectomy had positive margins, but negative lymph nodes.
  - Treated with Adriamycin and taxol
  - Mastectomy
  - Adalimumab held/ maintained on entocort during initial chemotherapy (did well)
  - Initiation of vedolizumab post chemotherapy when symptoms and fecal calprotectin increased
- Colonoscopy with Rutgeert's I0 at 1 year after vedolizumab initiation
- No residual tumor as of 3 years, considered in cancer remission

Case

- Presents with increased bowel movement frequency, and new perirectal pressure and drainage
- Colonoscopy performed: Rutgeert's I2 and active perianal fistula
- Abscess drainage and seton placed by colorectal surgery





Case

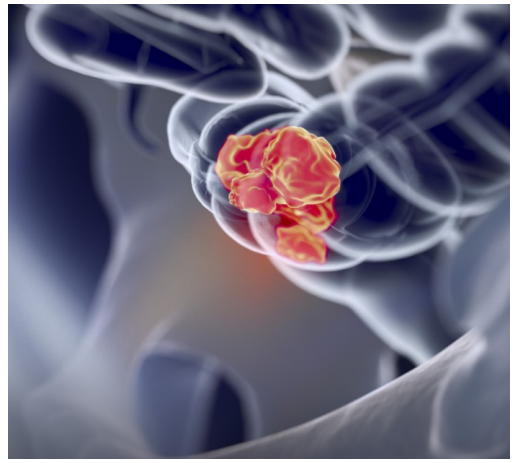
- What therapy would you select now?
- Would you have concerns about anti-TNF agents?
- Would you need combination therapy?

Breast Cancer Recurrence with Anti-TNF

- 3 retrospective cohorts in Medicare included women with RA and IBD who underwent surgery for primary breast cancer
- Recurrent cancers 1 year after first were identified
- Models to examine the risk associated with MTX, thiopurines, anti-TNF
  - 20.3 and 19.6 per 1,000 person-years in methotrexate users and nonusers
  - 32.3 and 17.6 per 1,000 person-years in thiopurine users and nonusers
  - 22.3 and 19.5 per 1,000 person-years in anti-TNF users and nonusers
- Risk of breast cancer recurrence by specific drug:
  - MTX – HR 1.07, 95% CI 0.67-1.69
  - Anti-TNF : HR 1.13, 95% CI 0.65-1.97
  - Thiopurines: HR 2.10, 95% CI 0.62-7.14

Mamtani R, et al. *Arthritis Rheumatol.* 2016 Oct;68(10):2403-11.

Proposed Algorithm : IBD and Cancer Recurrence



*Avoid IS associated with the risk of prior cancer. The longer the IS is held, the lower the risk of cancer recurrence.

**Hormonal therapy is associated with IBD flare

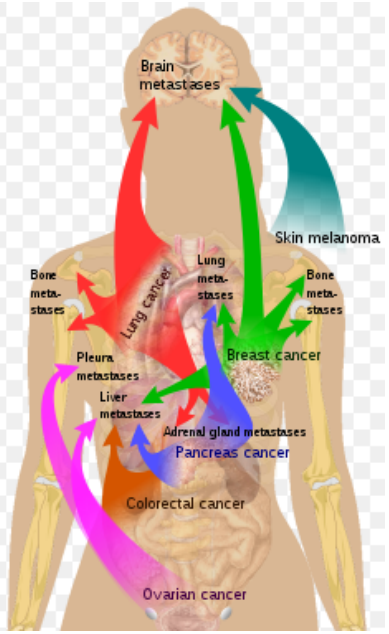
Bernheim O, et al. Gut. 2013 Nov;62(11):1523-8.

Back to the case….

- Restarted adalimumab
- Level checked post-load at the time of first maintenance to ensure no evidence of antibodies (appropriate – 18, no antibodies)
- Seton left in place, reduced drainage with the addition of the adalimumab
- Plans to repeat colonoscopy 6 months after initiation of adalimumab
- Standard follow up with her oncologist

Outline: IBD and Cancer

- Epidemiology of malignancy in IBD
- Risks of malignancy associated with therapies
  - Have the new biologics changed the landscape?
- Recurrence of malignancy
  - If you have cancer, what treatment?
  - Example case
- **Risk communication with patients on malignancy**
- Role of prevention of malignancy in IBD



Risk communication

Absolute risk of a disease is your risk of developing the disease over a time period; expressed in different ways

- 1 in 10 risk
- 10% risk
- 0.1 risk

Relative risk is used to compare the risk in two different groups of people – need to know the absolute risk to frame this risk

- RR of 10
- 10 fold increased risk

Clear Communication of Risk

Absolute risks better than relative risk

Avoid decimals (0.06%)

Keep common denominators (x/10,000)

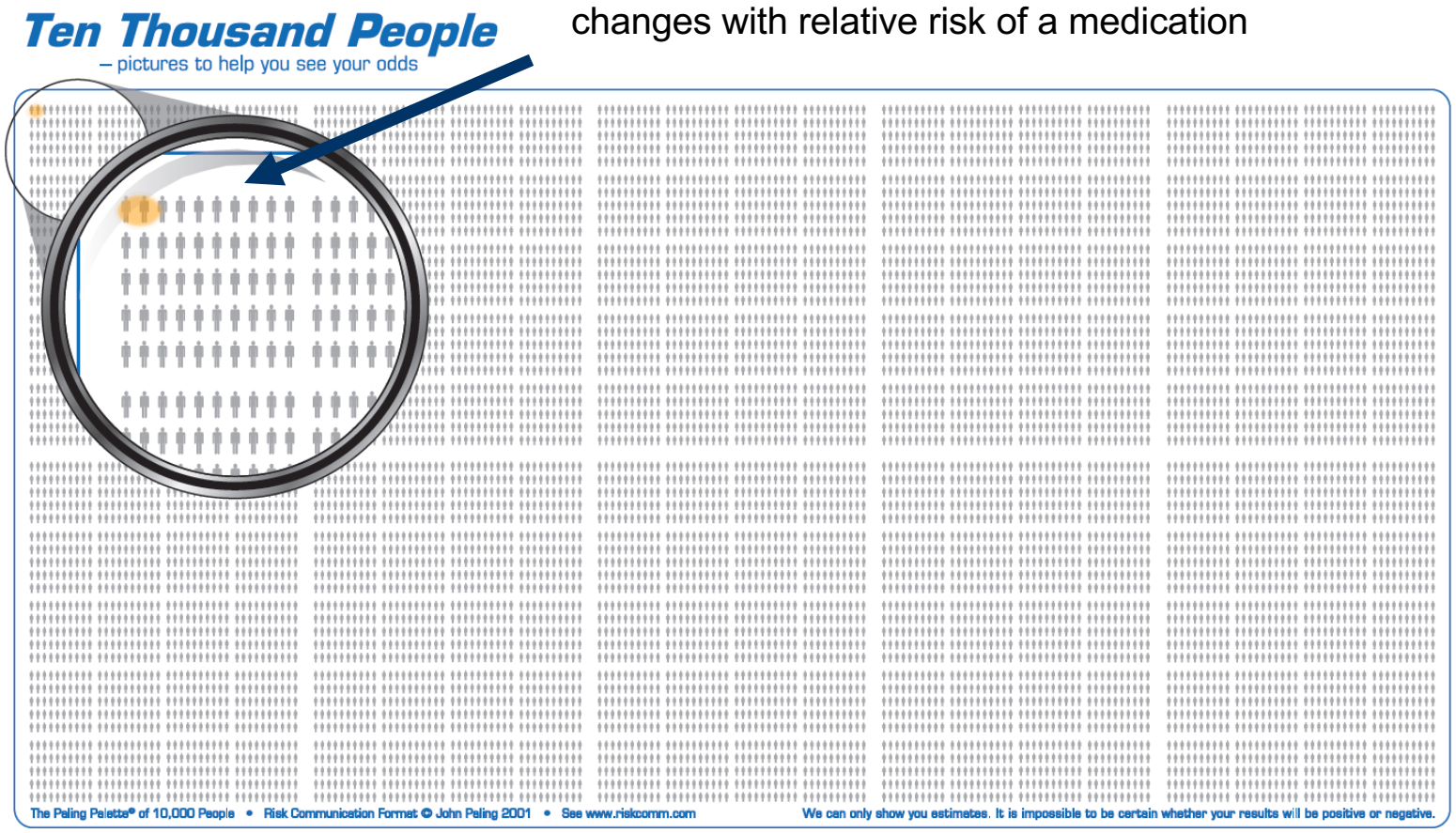
Visual aids help (turn numbers into pictures)

Give perspective to other disease & life risks

Fagerlin et al. Am J Health Behav 2007.
Peters et al. Health Affairs 2007.

Risk Communication: Absolute Risk

Highlight the absolute risk, and demonstrate how it changes with relative risk of a medication



Courtesy Corey Siegel MD

Malignancy Risks in IBD: Absolute Values

Increased risk of NMSC

- Absolute risk 73/10,000

Increased risk of melanoma

- Absolute risk 6/10,000

Increased risk of colorectal cancer

- Absolute risk 60/10,000

Increased risk of lymphoma

- Absolute risk on combination therapy anti-TNF and thiopurine 6/10,000
- Absolute risk on anti-TNF or thiopurine monotherapy 4/10,000
- Absolute risk of HSTCL overall 0.2/10,000, in men <35 on combo therapy 3/10,000

Risks of skin cancer persist after discontinuation of thiopurines, risks of lymphoma return to baseline

Outline: IBD and Cancer

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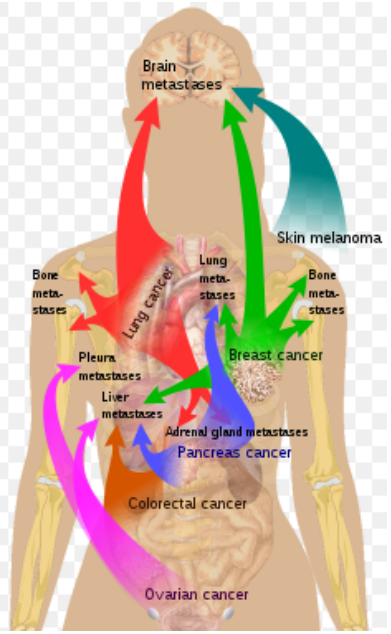
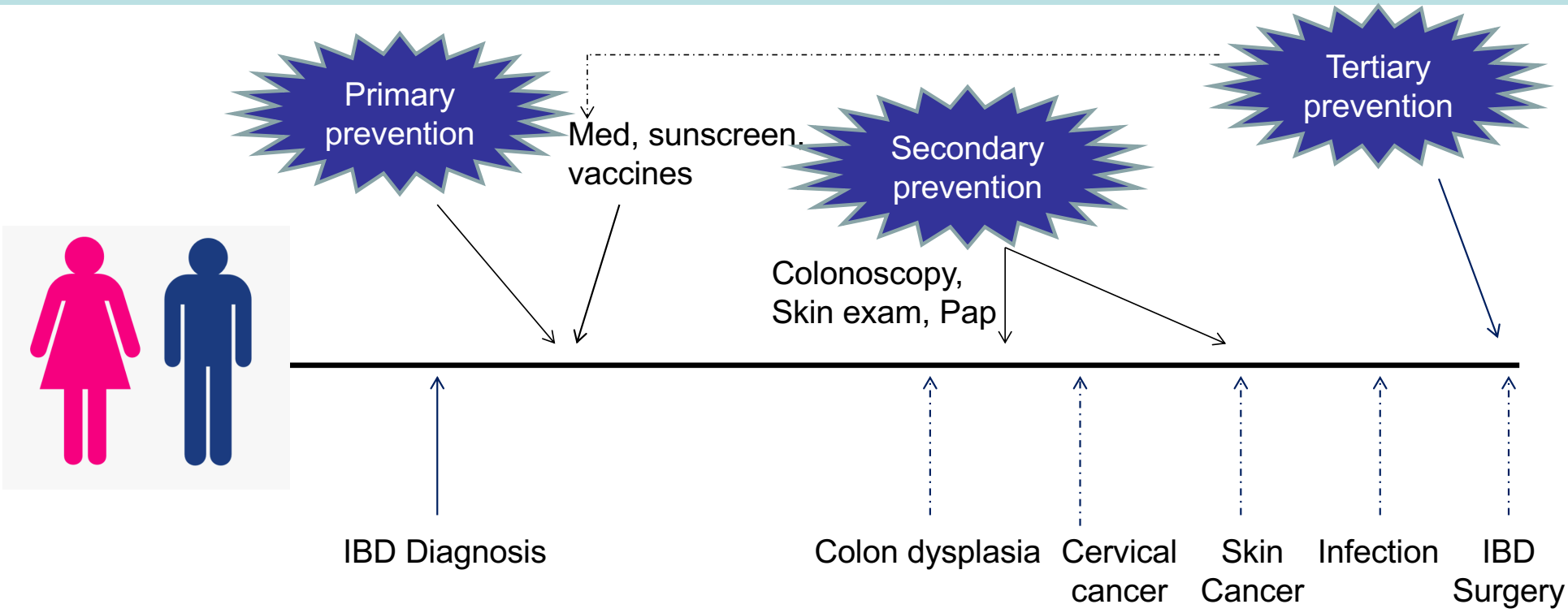


Role of Prevention in IBD: 3 Types



Summary

- Patients with IBD are at increased risk for malignancy
- As effective treatments have become available, GI malignancies have decreased while extra-intestinal cancers have remained stable
- Thiopurines and anti-TNF's have been associated with both lymphoma risk and skin cancer risk
- Risks of recurrence of cancer in IBD differ by initial type of malignancy
- Limited data available thus far are reassuring as to risks of recurrence with immunosuppressive IBD therapies
- Risk-benefit communication with patients is key, using absolute numbers
- Focus on preventive strategies early

UNC Multidisciplinary IBD Center