SLE AND CANCER: DOUBLE TROUBLE

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LEARNING OBJECTIVES

- Malignancy risk in adult and pediatric SLE
  - Hematologic
  - Other
- Review a few potential factors mediating risk
  - Immunosuppressive therapy
  - Smoking
  - Shared genetic susceptibility to SLE and malignancy
- Discuss possible recommendations
  - Immunosuppressive therapy counselling
  - Malignancy screening in SLE

CANCER RISK IN ADULT SLE

- Multi-centre clinical cohort
- Compare observed/ expected ➔SIR
- Cancers observed
  - Linked clinical cohorts to regional tumor registries to detect cancer
- Cancers expected
  - Multiply person-years in cohort by geographically-matched age, sex, calendar-year specific cancer rates from the same regional tumor registries

Bernatsky S, *et al. Arthritis Rheum.* 2005;52:1481-90.
Bernatsky S, *et al. J Autoimmun*. 2013;42:130-5.

OVERALL CANCER RISK IN ADULTS WITH SLE

- 30 centres, 1958–2009
- 16,409 patients- (90% female)
- 121,283 patient-years
- 5 cancers per 1,000 or 1 in 200

Malignancy	Observed	Expected	SIR	95% CI
Total	644	566	1.14	1.05, 1.23

HEMATOLOGIC CANCER RISK IN ADULTS WITH SLE

Malignancy	Observed	Expected	SIR	95%CI
All Heme	111	37	3.02	2.48, 3.63
NHL	76	17	4.39	3.46, 5.49
HL	7	3.1	2.28	0.92, 4.70
Leukemia	18	10	1.75	1.04, 2.76
Myeloma	10	5.3	1.88	0.90, 3.46

Total cancers, SLE duration					
Years	**O**	**E**	**SIR**	**95%CI**	
<1	**59**	**26.9**	**2.20**	**1.67**	**2.83**
1–4	**148**	**117.4**	**1.26**	**1.07**	**1.48**
5–10	151	141.8	1.06	0.90	1.25
10–19	189	179.9	1.05	0.91	1.21
>20	97	97.8	0.99	0.80	1.21
Hematological cancers, SLE duration					
Years	**O**	**E**	**SIR**	**95%CI**	
<1	**10**	**1.7**	**5.82**	**2.79**	**10.70**
1–4	**32**	**7.5**	**4.24**	**2.90**	**5.99**
5–10	**21**	**9.2**	**2.27**	**1.41**	**3.48**
10–19	**36**	**11.7**	**3.09**	**2.16**	**4.28**
>20	12	6.4	1.88	0.97	3.29

CANCER RISK IN PEDIATRIC SLE

- 12 centres, Observation interval 1974–2009
- 1,168 patients, 84% female, 8,839 patient-years
- Mean age at entry 13 years

Total and Hematologic Cancers

Malignancy	Observed	Expected	SIR	95% CI
Total	14	3.39	4.13	2.26, 6.93
NHL	3	0.57	18.6	3.84, 54.4

. Bernatsky S, *et al*. *J Rheumatol.* 2017

CANCER EVENTS IN PEDIATRIC SLE

- Three NHL cases
- Two head and neck squamous cell carcinomas (tongue and nasopharynx)
- One each of papillary thyroid cancer, glioblastoma, breast cancer, four others whose morphology and histology codes were indeterminate.
- Stratifying by sex, the SIR for all cancers was 6.26 (95% CI 1.29, 18.28) in males and 3.78 (95% CI 1.89, 6.76) in females.
- For cancer overall, stratifying results according to person-time contributed within age groups, the SIR was 3.29 (95% CI 0.68, 9.62) for events and person-time occurring up to age 20, which was similar to the SIR for events and person-time occurring after the age of 20 (SIR 4.44, 95% CI 2.22, 7.94).

TOTAL CANCERS SIRS IN PEDIATRIC-ONSET SLE ACCORDING TO SLE DURATION

SLE Duration (years)	Observed	Expected	SIR	95% CI
<1	2	0.1	15.2	1.8, 54.9
1–4	1	0.6	1.8	0.0, 9.9
5–9	1	0.6	1.7	0.0, 9.6
10–19	8	0.9	9.2	4.0, 18.2
20+	2	0.7	3.1	0.4, 11.1

WHY IS NHL INCREASED IN SLE?

- Predominance of DLBCL
  - Most arise from activated B-cells (non-germinal centre cells), possibly supporting a role for chronic immune stimulation (Tessier-Cloutier, B *et al.* USCAP. 2017)
  - Over-expression of APRIL/BAFF in SLE-related DLBCL
  - Abnormal immune stimulation leads to dysregulated lymphocyte proliferation
    - Increases possible translocation and juxtaposition of oncogenes beside genes regulating immune function.
    - May be a key step in malignant transformation of lymphocytes in conditions like SLE?
- Risk greatest earlier in disease
  - Suggesting role for disease activity and immune dysregulation rather than immunosuppressives?

LYMPHOMA RISK: ACTIVITY VERSUS DRUGS

- To determine if disease activity and/or treatment increases lymphoma risk
- Case-cohort design
  - Nested within international study
  - Involved 21 cohorts
  - Cases = SLE patients with lymphoma
  - Controls = SLE patients without lymphoma; randomly sampled from each cohort

Bernatsky S, *et al. Ann Rheum Dis*. 2008;67:74-9.
Bernatsky S, *et al. Ann Rheum Dis*. 2014;73:138-42.

FULLY ADJUSTED MODEL

Case-cohort Lymphoma, n=75	HR	95% CI
Male	2.7	1.4, 5.3
Age (years)	1.05	1.01, 1.13
White	0.9	0.5, 1.6
Sjogren's	1.8	0.9, 3.6
Steroids ever	0.8	0.2, 2.4
Cyclophosphamide ever	2.8	0.9, 9.0
Azathioprine ever	0.8	0.3, 2.2
Methotrexate ever	0.7	0.3, 1.8
Mycophenolate ever	1.5	0.6, 3.7
Antimalarials ever	1.6	0.8, 3.0
Disease activity (high)	0.7	0.4, 1.3

LUPUS-RELATED SINGLE NUCLEOTIDE POLYMORPHISMS AND RISK OF DIFFUSE LARGE B-CELL LYMPHOMA

- Using data from a recent lymphoma GWAS, we assessed whether certain lupus-related single nucleotide polymorphisms (SNPs) were also associated with DLBCL.
- GWAS data on European Caucasians from the International Lymphoma Epidemiology Consortium (InterLymph) provided a total of 3,857 DLBCL cases and 7,666 general-population controls.
- 28 SLE-related SNPs investigated
- The two lupus-related SNPs most convincingly associated with risk of DLBCL included the CD40 SLE risk allele rs4810485 on chromosome 20 and the HLA SLE risk allele rs1270942 on chromosome 6p21.33.
  - In SLE the strongest HLA association is for the Class II allele DRB1*0301.
  - This allele is in strong linkage disequilibrium with HLA-B*0801 in Caucasians so we are likely tagging the same HLA effect.

SLE RELATED SNPS AND ODDS RATIO FOR DIFFUSE LARGE B CELL LYMPHOMA

Gene	Chromosome	SNP	DLBCL OR	95% CI
CD40	20	rs4810485	1.09	1.02-1.16
HLA	6	rs1270942	1.17	1.01-1.36
TNFSF4	1	rs2205960	1.07	1.00-1.16
IRF5	7	rs12537284	1.08	0.99, 1.18

Bernatsky, S. *Lupus Science & Medicine.* 2017: In Press.

WHAT ABOUT TNFAIP3?

- TNFAIP3 related to the A20 protein important in nuclear factor κ B activation
  - The majority of Sjögren's patients with Primary Sjögren's and mucosa-associated lymphoid tissue (MALT) lymphoma have either germline polymorphisms of TNFAIP3, or somatic alterations of the gene within the lymphoma tissue.
  - Polymorphisms of TNFAIP3 are common to both RA and Hodgkin's lymphoma.
- TNFAIP3 SNP rs7749323 is linked to lupus but not specifically for lupus-related DLBCL
  - This may be a power issue, or may reflect the importance of different pathways for different hematological risk profiles across different autoimmune rheumatic diseases ·

Nocturne G, Boudaoud S, Miceli-Richard C, et al. Germline and somatic genetic variations of TNFAIP3 in lymphoma complicating primary Sjögren's syndrome. Blood. 2013;122(25): 4068-4076. doi:10.1182/blood-2013-05-503383.

Okada Y, Wu D, Trynka G, et al. Genetics of RA contributes to biology and drug discovery. *Nature*. 2014;506.

OTHER CANCERS, RISK IN ADULTS WITH SLE

Malignancy	SIR	95% CI
Lung	1.30	1.04, 1.60
Thyroid	1.76	1.13, 2.61
Hepatobiliary	1.87	0.97, 3.27
Bladder	1.25	0.74, 1.97
Gastric	1.19	0.65, 2.00
Colorectal	0.88	0.66, 1.15
Pancreas	0.90	0.43, 1.65
Prostate	0.65	0.32, 1.16
Melanoma	0.67	0.34, 1.20

WHAT DRIVES LUNG CANCER RISK IN SLE?

- Case-cohort study nested within international malignancy cohort study, lung cancer HR for smoking was 6.4 (95% CI 2.4, 16.6)
- SLICC inception cohort: univariate hazard regression suggested cancer events were more common in whites, older patients, and smokers.
- For lung cancer specifically, adjusted hazards showed age and smoking were clearly associated with lung cancer risk.
- No clear link with anti-dsDNA antibodies; would be interesting to look at other auto-antibodies (e.g. anti-CENP-F, which may be positively associated with lung cancer in the general population)

Case-cohort Lung cancer , n=49	Adjusted HR	95% CI
Calendar year	1.03	0.97, 1.09
Age	1.09	1.06, 1.12
Male	1.13	0.46, 2.74
White	2.10	0.56, 7.93
Smoking (ever)	6.35	2.43, 16.6
dsDNA positivity (average)	0.42	0.11, 1.57
Steroids ever	0.60	0.17, 2.15
Cyclophosphamide >6 g	0.17	0.03, 1.00
Azathioprine ever	0.68	0.08, 5.63
Methotrexate ever	1.14	0.32, 4.02
Mycophenolate ever	1.43	0.39, 5.20
NSAIDS ever	0.57	0.25, 1.26
Antimalarial use >5 yrs	0.55	0.20, 1.51
SLE Activity top quartile	1.29	0.64, 2.58
Pulmonary fibrosis	2.41	0.63, 9.22

WHAT DRIVES THYROID CANCER RISK IN SLE?

Five SLE patients with papillary thyroid cancer and 148 SLE controls without cancer

Thyroid autoimmunity (anti-thyroglobulin antibodies, AbTg, and anti-thyroperoxidase antibodies, AbTPO) was more common in thyroid cancer: (80%) versus cancer-free subjects(31%)

TSH higher (and T3, T4) lower in SLE cancer cases versus SLE non cancer cases

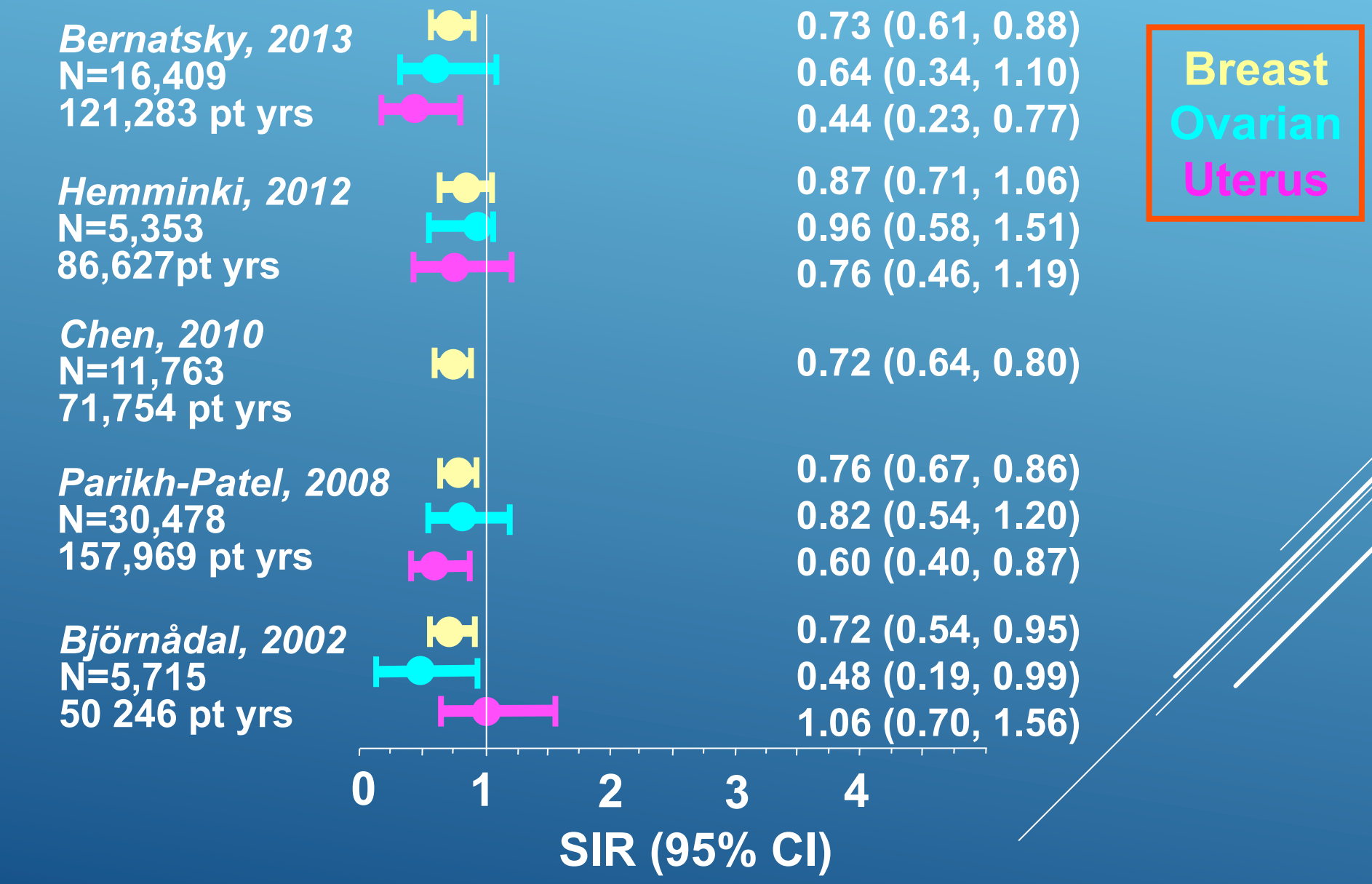
Benign thyroid nodules also increased in SLE …..

Antonelli, et al *Journal Clin Endocrinology & Metabolism*, 2010: 95

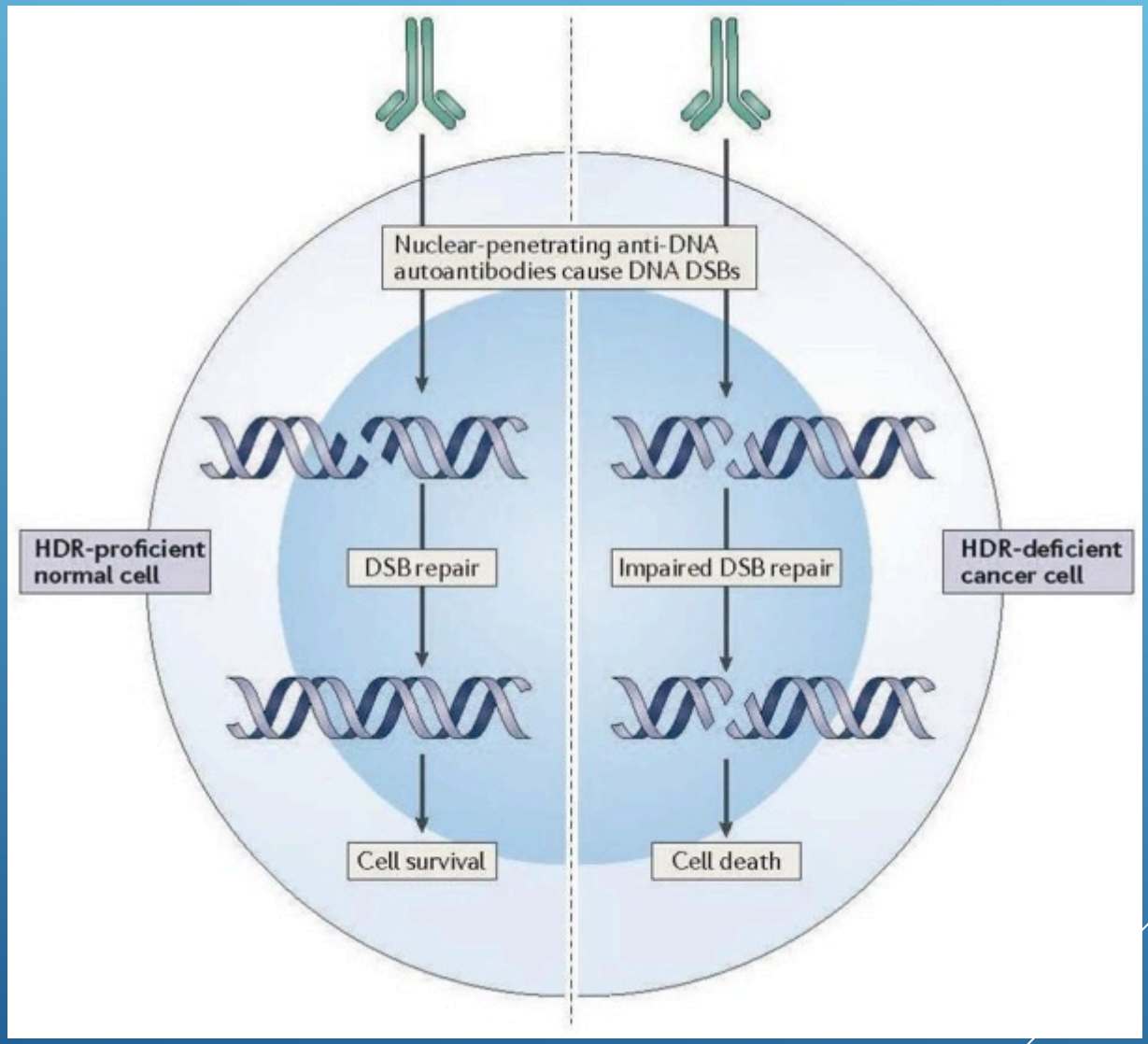
REPRODUCTIVE CANCERS IN SLE STANDARDIZED INCIDENCE RATIOS

Malignancy	Observed	Expected	SIR	95%CI
Breast	114	155	0.73	0.61, 0.88
Uterus	12	27	0.44	0.23, 0.77
Ovary	13	20	0.64	0.34, 1.10
Cervix	21	17	1.27	0.78, 1.93
Vagina	2	0.5	3.80	0.46, 13.7
Vulva	7	2	3.78	1.52, 7.78

RISK OF REPRODUCTIVE CANCERS

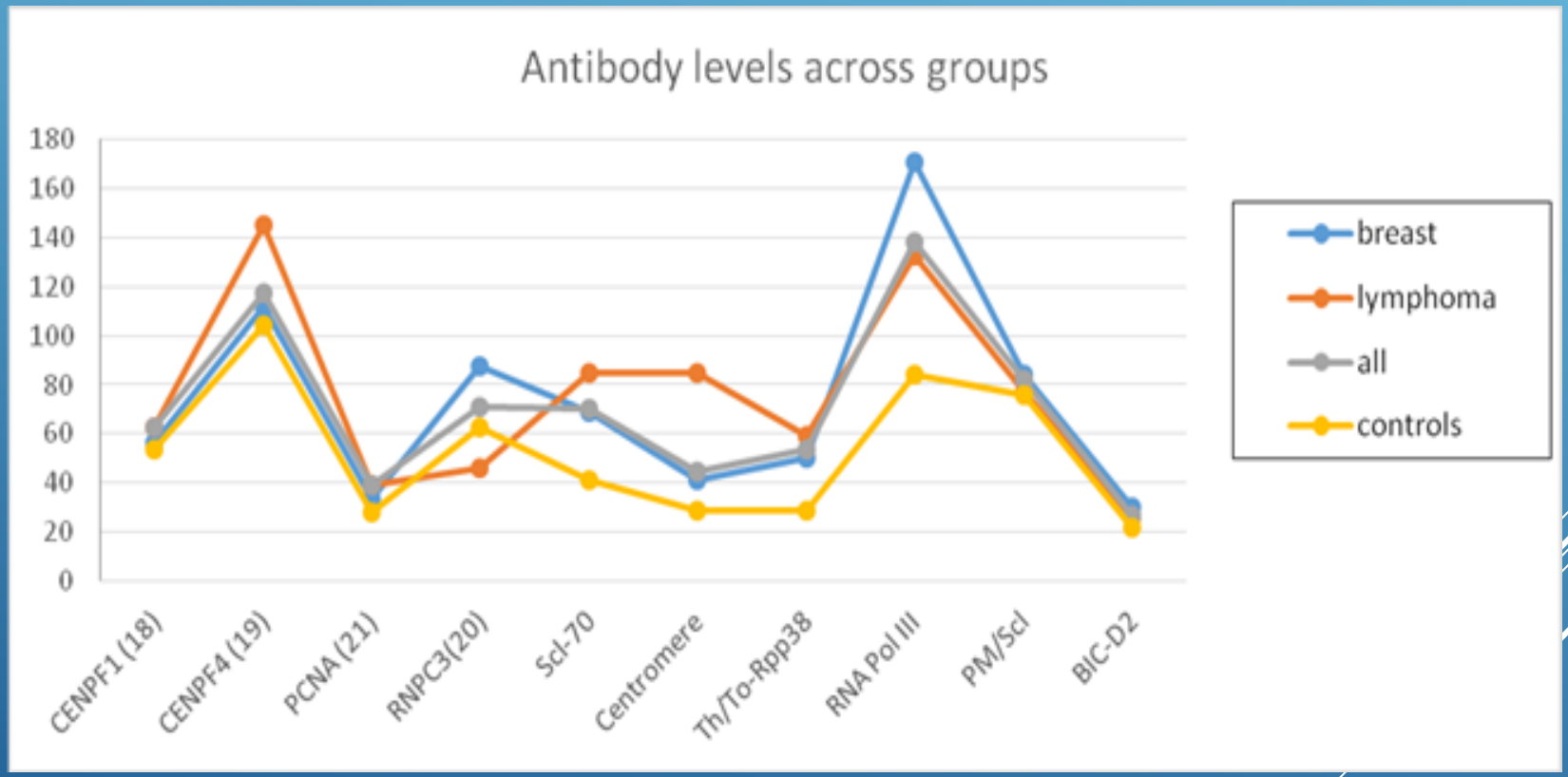


NUCLEAR-PENETRATING AUTOANTIBODIES AND CELL DEATH



Noble PW, *et al. Nat Rev Rheumatol*. 2016;12:429-34.

TUMOR-RELATED AUTO-ANTIBODIES AND CANCER IN SLE: A CASE-CONTROL STUDY FROM A SINGLE CENTRE



11 lymphoma, 8 breast, two endometrial, 1 each colon and kidney.

SLE-RELATED SNPS AND OR FOR BREAST CANCER IN BREAST CANCER GWAS

Chromosome	SNP	Breast Cancer OR	Breast Cancer P-value
2q32.3	rs7574865	0.9948	0.8917
3p14.3	rs6445975	1.0911	0.0097
4q24	rs10516487	0.9938	0.8516
5q33.3	rs2431697	1.0095	0.7618
16p11.2	rs9888739	0.9076	0.0499

Bernatsky S, *et al. Lupus*. 2012;21:896-9.

CERVICAL DYSPLASIA

- Multiple studies have demonstrated an increased risk of cervical dysplasia and of high-grade squamous intraepithelial lesions in SLE patients
  - e.g 2014 meta-analysis (Zard *et al.* 2014) pooled odds ratio for high-grade squamous epithelial lesions in SLE versus controls was 8.66, 95% CI 3.75-20.0
- A recent review of cancer screening recommendations in SLE found no original research directly comparing cancer screening strategies in SLE, although generally, authors recommend adherence to general population screening measures, particularly cervical screening
- Recent CRA/CaNIOS recommendations “All female adults with SLE who are or have been sexually active, annual cervical cancer screening at least up to age 69.” (Conditional, low evidence)

SUMMARY

- Overall cancer risk in SLE versus general population
  - Increased – slightly
- Hematological malignancies
  - Highly increased
- Lung, Thyroid
- Breast, endometrial, ovarian
  - Decreased

FACTORS POTENTIALLY ASSOCIATED

- Immunosuppressive exposure
  - Cyclophosphamide – potential association with hematologic malignancies
- Shared genetic susceptibility to SLE and lymphoma?
- Smoking & lung cancer
- HPV? Cervical neoplasia, vulvar/vaginal…

PRACTICE IMPLICATIONS

- No personal cancer history
  - Use immunosuppressives as clinically indicated
  - Patient education regarding magnitude of risks
  - Limit cyclophosphamide to IV for a few months, use MESNA and hydration to avoid bladder toxicity
- Remote cancer history
  - Proceed as above ?
  - Avoid cyclophosphamide?
- Recent history of malignancy
  - No data (aside from antimalarials being ok)
  - Discuss with oncology
  - Rituximab may be an option in severe disease?

PRACTICE IMPLICATIONS

- Malignancy screening
  - Patients should follow general population recommendations
  - Screening for cervical dysplasia especially important (particularly with immunosuppressive exposures
  - Yearly urine cytology if previously exposed to cyclophosphamide
  - Yearly skin evaluations?
- Other considerations
  - HPV vaccination?

Tessier-Cloutier B, *et al. Lupus.* 2015;24:781-787
Mosca M, *et al. Ann Rheum Dis.* 2010;69:1269-1274
Grein IHR, *et al. Pediatric Rheumatology*. 2016;12:1-8.

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Median levels of antibodies in each group (expressed in fluorescence units)

	CENPF1	CENPF4	PCNA	RNPC3	Scl-70	Centromere	Th/To-Rpp38	RNA Pol III	Th/To-Rpp25	PM/Scl
Breast	56.5	111.5	33.5	87.5	69	41.5	50.25	170.5	25	84.25
NHL	63	145	39	46	85	85	59	132.5	21	77
All cancers	63	117	39	71	70	45	53.5	138	25	82
SLE controls	54	104	28	63	41	29	29	84	20	76

SLICC COHORT: CANCER RISK

- We also looked at baseline tumor-related auto-antibodies (e.g. anti-centromere protein, CENP) in the SLICC inception cohort
  - Anti-CENP (B-type may be protective for breast cancer)

*Madrid et. Al. Autoantibodies in breast cancer sera BMC Cancer. 2015;15:407.

- Baseline anti-CENP-B was found in 1.9% (95% CI 1.1,2.9) of cancer-free patients, and none of the cancer cases.

ACR poster 1606 Monday: Cancer in an SLE Inception Cohort: Smoking May out-Perform Tumor Markers As a Risk Predictor.