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Enhancing the Ability to Diagnose, Interpret and Apply Best Treatment Options for Cutaneous Lymphomas

Increased incidence of second primary malignancies in patients with primary cutaneous B-cell lymphomas: a SEER population study

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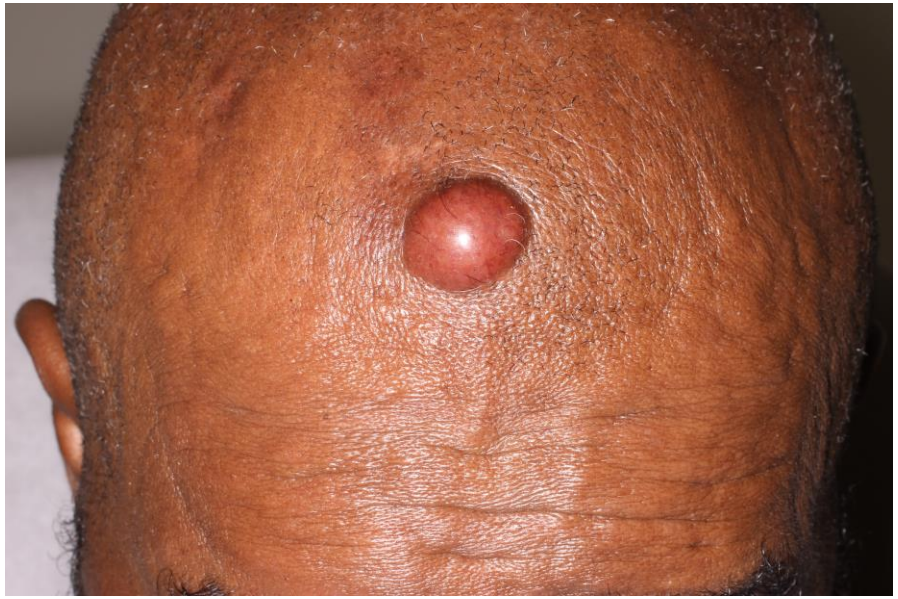
Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Introduction

- Primary cutaneous B-cell lymphomas (PCBCL) are extra-nodal non-Hodgkin B-cell lymphomas originating in the skin.
- PCBCL has an incidence of 4 per million persons per year, most frequently in non-Hispanic whites, males, and individuals over the age of 50.[1,2]
- PCBCL variants by order of frequency and prognosis include:
    - Primary cutaneous follicle center lymphoma (indolent)
    - Primary cutaneous marginal zone lymphoma (indolent)
    - Primary cutaneous diffuse large B-cell lymphoma, leg type (intermediate)



Primary cutaneous follicular center lymphoma

1. Korgavkar and Weinstock 2014, *JID*
2. Bradford et al. 2009, *Blood*

Image: Correia et al. 2022, *Haematologica*

Introduction

- 5-year survival rates vary between ~60% for more aggressive subtypes and 95%-99% for indolent subtypes.[2,3]
- non-Hodgkin's lymphomas are associated with the development of subsequent malignancies.[4]
- Small studies of 36, 51, 98, and 144 PCBCL patients have noted differing observed rates of second malignancies following PCBCL diagnosis.[5-7]
- No study to date has evaluated the risk of developing subsequent solid malignancies in PCBCL patients.

2. Bradford et al. 2009, *Blood*
3. Chan et al. 2017, *BJD*
4. Travis et al. 1993, *J Natl Cancer Inst.*
5. Gomez Sanchez et al. 2019, *An Bras Dermtol.*
6. Kim et al. 2019, *Ann Dermatol.*
7. Avallone et al. 2022, *Acta Derm Venereol.*

Objectives

Primary

- To calculate the risks of common solid tumor malignancies following PCBCL diagnosis

Secondary

- To identify at-risk PCBCL patient subsets through risk stratification by sex, treatment history, and age of and latency after PCBCL diagnosis

Methods

- Retrospective, population-based cohort study utilizing the Surveillance, Epidemiology, and End Results - 17 registries (SEER-17) from 1/2000-12/2020
    - SEER-17 is a national cancer registry containing the data of 9.2 million cancer patients
- N = 5,435 PCBCL patients
- Analysis using SEER*Stat Version 8.4.0.1 (National Cancer Institute, Bethesda, MD)
    - Relative risk estimated with standardized incidence ratios (SIR)
    - Stratified risk by age, sex, and latency since PCBCL diagnosis
    - Statistical significance based on 95% confidence intervals (CI)
    - Clinical significance based on ≥ 10 observed patients with the second malignancy[8]

8. Goyal et al. 2020, *J Am Acad Dermatol.*

Baseline Demographics

- N = 5,435 PCBCL patients

- Majority:
  - Male (n = 3,127; 57.5%)
  - White (n = 4,624; 85.1%)
  - 60-69 years of age (n = 1,233; 22.7%)
  - Head and neck presentations (n = 2,539; 46.7%)
  - PCFCL (n = 1,928; 35.5%)
  - Initially treated with radiotherapy (n = 2,487; 45.8%)

Characteristic	Total, n (%)	Male, n (%)	Female, n (%)
PCBCL patients	5,435	3,127 (57.5)	2,308 (42.5)
Race			
White	4,624 (85.1)	2,681 (49.3)	1.943 (35.8)
Black	294 (5.4)	153 (2.8)	141 (2.6)
AIAN	25 (0.5)	9 (0.2)	16 (0.3)
AAPI	325 (6)	184 (3.4)	141 (2.6)
Unknown	167 (3)	100 (1.8)	67 (1.2)
Age at Diagnosis			
≤39	667 (12.3)	461 (8.5)	206 (3.8)
40-49	631 (11.6)	416 (7.7)	215 (3.9)
50-59	1,083 (19.9)	630 (11.6)	453 (8.3)
60-69	1,233 (22.7)	732 (13.5)	501 (9.2)
70-79	996 (18.3)	528 (9.7)	468 (8.6)
80+	825 (15.2)	360 (6.6)	465 (8.6)
Anatomic Site			
Head and neck	2,539 (46.7)	1,507 (27.7)	1,032 (19)
Trunk	983 (18.1)	555 (10.2)	428 (7.9)
Upper limbs	759 (14)	435 (8)	324 (6)
Lower limbs	515 (9.5)	254 (4.7)	261 (4.8)
Multisite / NOS	639 (11.7)	376 (6.9)	263 (4.8)
PCBCL Subtype			
PCFCL	1,928 (35.5)	1,162 (21.4)	766 (14.1)
PC-DLBCL	1,279 (23.5)	680 (12.5)	599 (11)
PCMZL	1,753 (32.2)	990 (18.2)	763 (14)
Other / unknown	475 (8.8)	295 (5.4)	185 (3.4)
Treatment			
Any radiation	2,487 (45.8)	1,478 (27.2)	1,009 (18.6)
Any chemotherapy	1,163 (21.4)	637 (11.7)	526 (9.7)
Any surgery	2,011 (37)	1,173 (21.6)	838 (15.4)

Results

- 847 PCBCL patients (16%) developed a subsequent malignancy, a **54% increase** compared to the general population
  - Thyroid cancers displayed the greatest increased risk (**127% increase**)
  - Kidney and renal pelvis cancers had a **54% increased risk**
  - Prostate cancers displayed the least increased risk (**29% increase**)

Malignancy	Obs	SIR (95% CI)
All Cancers	847	**1.54 (1.43 – 1.64)**
Thyroid	17	**2.27 (1.32 – 3.63)**
Kidney	30	**1.54 (1.04 – 2.20)**
Prostate	118	**1.29 (1.07 – 1.54)**
Bladder	40	1.21 (0.87 – 1.65)
Brain	7	1.20 (0.48 – 2.46)
Breast	60	1.11 (0.84 – 1.42)
Colon	49	0.99 (0.73 – 1.30)
Esophagus	5	0.78 (0.25 – 1.82)
Liver	16	1.05 (0.60– 1.71)
Lung	93	1.22 (0.98 – 1.49)
Melanoma	40	1.35 (0.96 – 1.83)
Oral Cavity	14	0.98 (0.54 – 1.64)
Pancreas	16	0.91 (0.52 – 1.47)
Stomach	10	1.10 (0.53 – 2.02)
Uterus	14	0.94 (0.50 – 1.61)

Results by Sex

- 6/15 tumors had sex-specific significance
- Females had increased risks of:
  - Thyroid cancers (206%)
  - Kidney cancers (113%)
  - Lung cancers (69%)
- Males had increased risks of:
  - Melanoma (49%)
  - Bladder cancers (42%)
  - Prostate cancers (29%)

Females	Obs	SIR (95% CI)
Thyroid	13	**3.06 (1.63 – 5.23)**
Kidney	11	**2.13 (1.06 – 3.81)**
Lung	48	**1.69 (1.25 – 2.24)**

Males	Obs	SIR (95% CI)
Melanoma	33	**1.49 (1.03 – 2.09)**
Bladder	39	**1.42 (1.01 – 1.94)**
Prostate	118	**1.29 (1.07 – 1.54)**

Results by Latency from PCBCL Diagnosis

- Risks for all second cancers peaked within the first year and then tapered
- Thyroid cancers had the highest increased risk within 1 year (**16.5-fold**)

	2mo– 1y		1y – 5y		5y – 10y		10y - 15y		15y+		Total	
Cancer	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	Exp
All Cancers	143	**2.49**	330	**1.5**	235	**1.41**	108	1.33	31	**1.21**	847	550
Thyroid	13	**16.52**	1	0.33	2	0.87	1	0.95	0	0	17	7.49
Bladder	4	1.21	19	1.48	10	1.00	4	0.79	3	1.80	40	32.94
Lung	12	1.49	39	1.27	25	1.09	14	1.27	3	0.88	93	76.23
Kidney	9	4.67	8	1.05	11	1.85	2	0.67	0	0	30	19.42
Melanoma	2	0.69	19	1.66	11	1.21	7	1.48	1	0.64	40	29.74

Results by Latency from PCBCL Diagnosis

- Females had a **21-fold** increased risk of thyroid cancer < 1 y
- Females within 5 years had increased risk of lung cancer
- Males within 5 years had increased risks of prostate, melanoma, and bladder cancers

	2mo– 1y		1y – 5y		5y – 10y		10y - 15y		15y+		Total	
Cancer	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	Exp
Female												
Thyroid	10	21.1	1	0.56	2	1.56	0	0	0	0	13	4.3
Lung	7	2.22	20	1.7	14	1.65	6	1.57	1	0.87	48	28.4
Kidney	2	3.58	5	2.35	4	2.56	0	0	0	0	11	5.2
Male												
Prostate	20	2.09	38	1.03	40	1.45	17	1.26	3	0.71	118	91.5
Melanoma	1	0.48	16	1.91	9	1.32	6	1.64	1	0.81	33	22.2
Bladder	4	1.48	18	1.7	10	1.19	4	0.92	3	2.09	39	27.5

Results by Age of PCBCL Diagnosis

- Second cancer risk decreases with age
- Patients in their 40s had a **3-fold** increased risk

	40-49		50-59		60-69		70-79		80+		Total	
Cancer	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	Exp
All Cancers	36	3.07	101	1.92	223	1.55	279	1.48	200	1.32	847	550
Thyroid	3	4.05	1	0.66	2	0.89	7	3.85	2	2.48	17	7.49
Bladder	0	0	3	1.81	9	1.41	16	1.33	12	0.95	40	32.94
Lung	1	1.77	4	0.83	23	1.29	39	1.3	26	1.14	93	76.23
Kidney	4	6.26	6	2.55	7	1.25	10	1.52	3	0.72	30	19.42
Melanoma	2	2.14	7	2.31	11	1.53	8	0.83	12	1.4	40	29.74

Results by Age of PCBCL Diagnosis

- Females in their 70s showed a **1.8-fold** increased risk of lung cancer
- Males in their 60s were at a **1.5-fold** risk of prostate cancer

	40-49		50-59		60-69		70-79		80+		Total	
Cancer	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	Exp
Female												
Lung	1	5.51	2	1.23	8	1.3	20	1.84	17	1.78	48	28.4
Thyroid	2	4.4	1	1.11	1	0.79	5	5.26	2	4.42	13	4.3
Kidney	2	15.85	1	1.96	1	0.74	6	3.54	1	0.68	11	5.2
Male												
Prostate	1	1.47	14	1.5	51	1.53	36	1.05	16	1.14	118	91.5
Melanoma	2	3.26	6	2.79	7	1.41	8	1.06	1.59	0.76	33	22.2
Bladder	0	0	3	2.12	9	1.65	15	1.46	12	1.18	39	27.5

Results by Treatment History of PCBCL

- All treatments increased second cancer risk for PCBCL patients
- Females who received chemotherapy had a **2.3-fold** increased lung cancer risk
- Males who received radiation had a **1.4-fold** increased risk of prostate cancer

	Chemotherapy		No/Unk Chemotherapy		Radiation		No Radiation	
Cancer	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR
PCBCL	217	1.71	625	1.47	398	1.47	433	1.58
Female								
Lung	17	2.25	232	1.49	20	1.56	27	1.76
Kidney	2	1.52	9	2.34	6	2.54	5	1.81
Thyroid	6	6.14	7	2.14	6	2.97	7	3.19
Male								
Prostate	25	1.22	92	1.30	64	1.37	53	1.23
Melanoma	1	0.22	32	1.82	17	1.51	14	1.32
Bladder	10	1.73	29	1.34	22	1.57	17	1.29

Results by Stage of Subsequent Cancer

- Most second cancers were found in early stages
- Females:
  - **4-fold** risk of localized thyroid
  - **3.4-fold** risk of localized kidney
  - **1.62-fold** risk of localized lung
- Males:
  - **1.34-fold** risk of localized prostate cancer

	Localized		Regional		Distant	
Cancer	Obs	SIR	Obs	SIR	Obs	SIR
All Cancers	476	1.54	27	1.26	89	2.06
Female						
Thyroid	10	3.85	0	0	0	0
Kidney	10	3.41	0	0	0	0
Lung	25	1.62	2	1.62	8	3.19
Male						
Prostate	68	1.34	3	0.91	10	1.48
Melanoma	19	1.47	2	2.5	0	0
Bladder	24	1.55	1	1	4	1.95

Summary

- PCBCL patients were at greater risk of 6 solid tumors: **thyroid, renal, lung, melanoma, bladder, and prostate**.
  - Neoplasm predisposition may be due to decreased immune surveillance[9]
  - Females: thyroid, kidney, and lung
  - Males: melanoma, bladder, and prostate
- All these cancers peaked in increased risk within 5 years of PCBCL diagnosis.
  - Females: thyroid within 1 year and lung within 5 years
  - Males: prostate, bladder, and melanoma within 5 years

9. Mazzetto et al. 2023, *Hematol Rep*.

Summary

- Overall, patients diagnosed in their 40s had the highest risks of all second cancers.
  - Females: lung in 70s
  - Males: prostate in 60s
- All investigated PCBCL therapies increased subsequent cancer risk.
  - Females: lung with chemotherapy
  - Males: prostate with radiotherapy
- Most second cancers were found in early stages.
  - Females: localized thyroid, kidney, and lung
  - Males: localized prostate

Clinical Implications

- Female PCBCL patients should adhere to the US Preventative Services Task Force (USPSTF) recommendations on screening for lung cancer.
- No USPSTF screening guidelines exist for melanoma, bladder, prostate, thyroid, and renal cancer for asymptomatic patients; these cancers should be monitored per clinical symptoms, provider judgment, and patient history.
- Patients with PCBCL should be counseled against preventable lifestyle factors like smoking cessation which further increases the risks of bladder and lung cancers.

9. Mazzetto et al. 2023, *Hematol Rep*.

Limitations

- Retrospective study design
- Limited number of PCBCL patients due to rarity of disease
- Population-level data has limited applicability to individuals
- Heterogeneity in the reporting of rare cancers
    - Broadly characterized as “PCBCL”

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Thank you!

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