AFRL

THE MISSILE COMMUNITY CANCER STUDY: EPIDEMIOLOGY REVIEW PHASE 2 RESULTS

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United State Air Force School of Aerospace Medicine (USAFSAM) Epidemiology Consult Service (ECS) Division

- Provides worldwide consultation services for public health surveillance, epidemiology, and preventive medicine.
- Offers rapidly deployable support for urgent and complex epidemiological investigations.
- Comprises a specialized team of military, civilian, and contract professionals, including:
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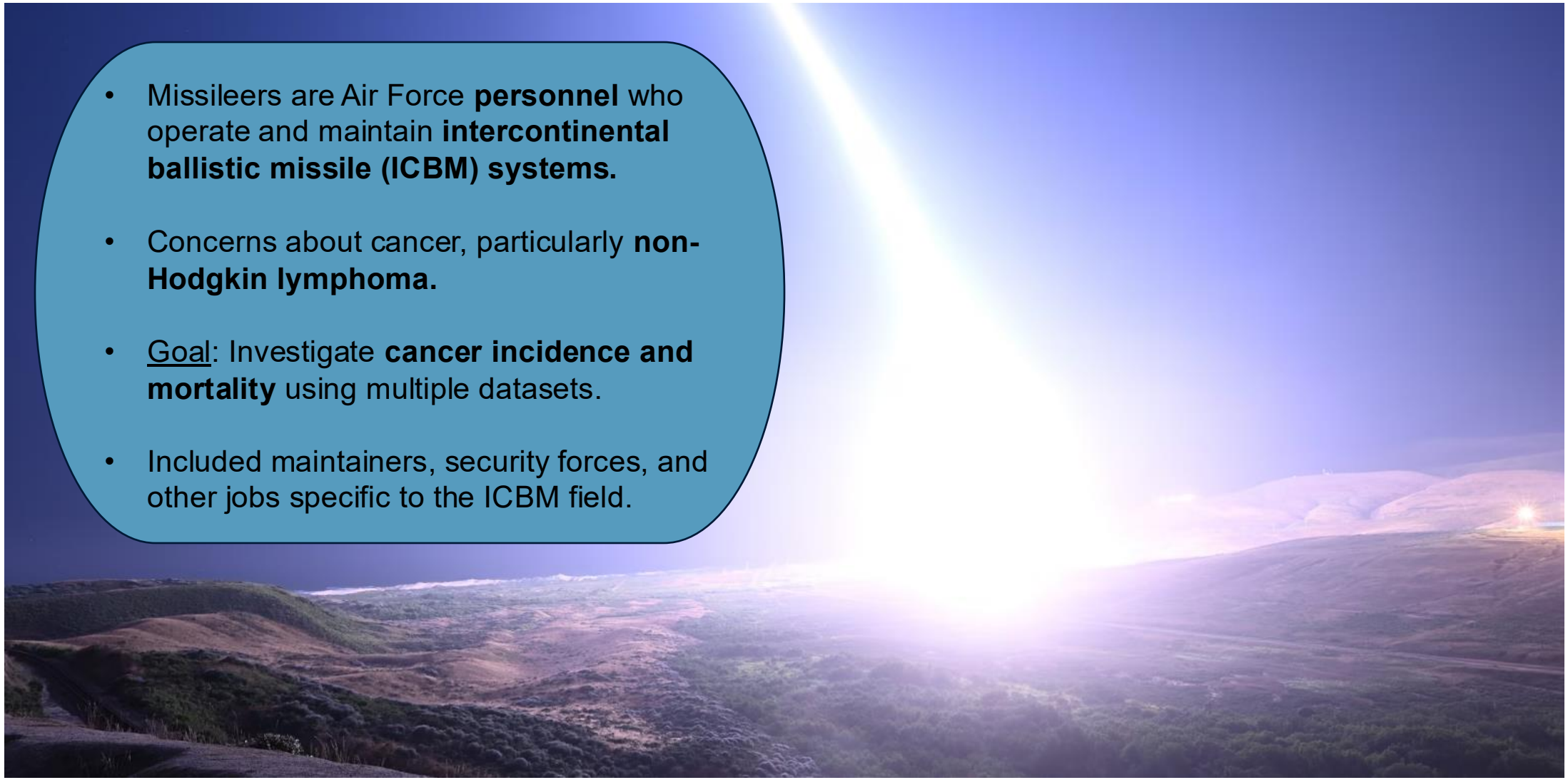
  - Epidemiologists
  - Biostatisticians
  - Data managers
- Delivers global epidemiological consulting in key health areas:
  - Community and behavioral health
  - Occupational and environmental health
  - Infectious and chronic diseases

Missile Community Cancer Study: Background/Methods

Background on the Missile Community (MC)



- Missileers are Air Force **personnel** who operate and maintain **intercontinental ballistic missile (ICBM) systems.**
- Concerns about cancer, particularly **non-Hodgkin lymphoma.**
- Goal: Investigate **cancer incidence and mortality** using multiple datasets.
- Included maintainers, security forces, and other jobs specific to the ICBM field.

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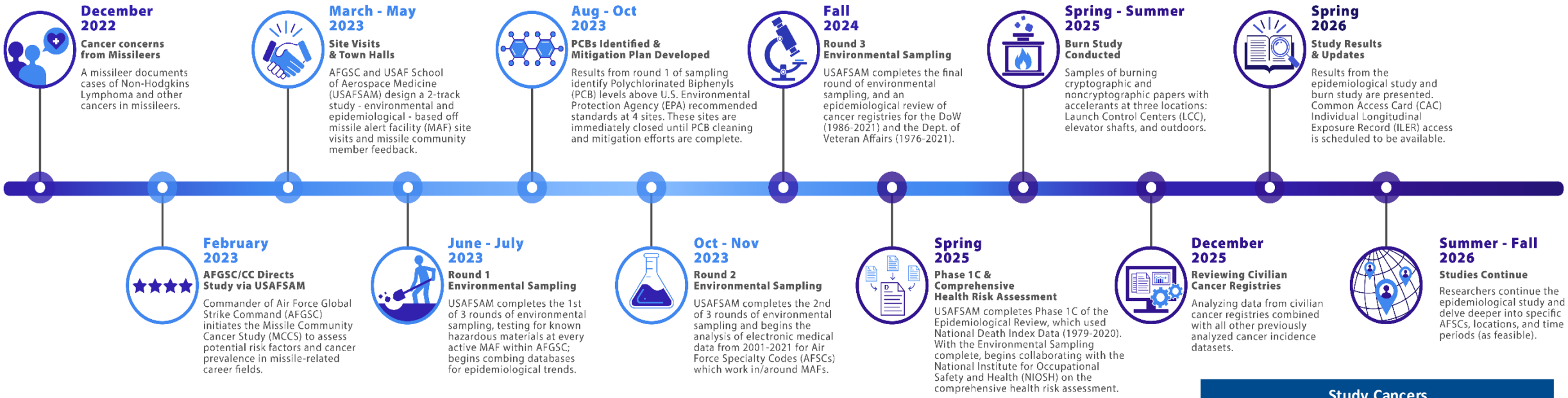
Missile Community Cancer Study (MCCS) Overview

Missile Community Cancer Study
Current Timeline



Epidemiology Review
Compare 14 common cancers in the general population to missile-related career fields using large government databases

- Data back to 1976
- Includes cohort of past/present missile community members

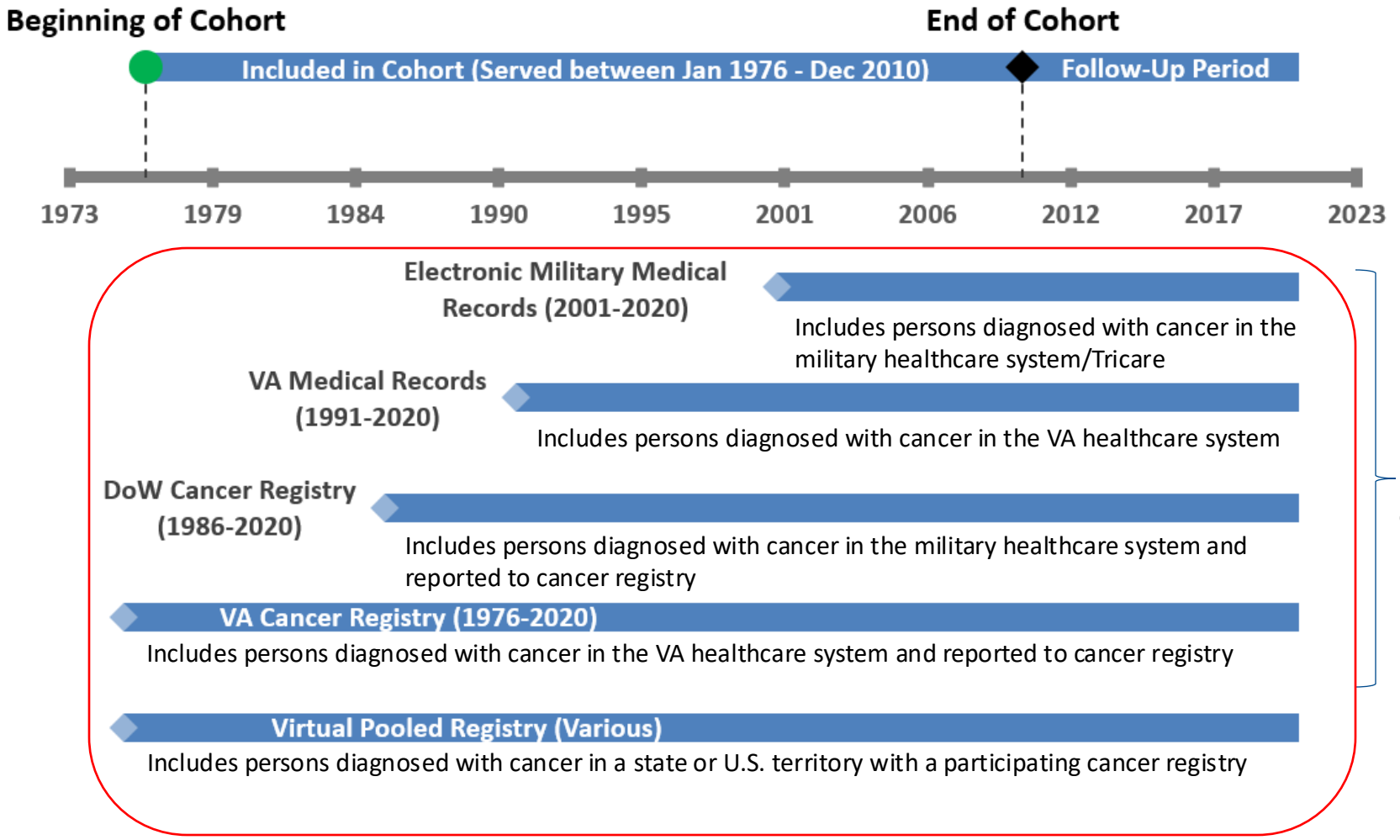
Environmental Sampling
Collect 3 seasonal rounds to assess for any chemicals, contaminants, or hazards

Study Cancers	
Breast (Male and Female)	Non-Hodgkin Lymphoma
Colon and Rectum	Ovarian
Hodgkin Lymphoma	Pancreatic
Kidney and Renal Pelvis	Prostate
Leukemia	Testicular
Lung and Bronchus	Thyroid
Melanoma of the Skin	Urinary Bladder

Cohort Creation

- All Active Duty (AD) Department of the Air Force (DAF) service members from 1976 to 2010
  - Used Duty Air Force Specialty Codes (DAFSC) to categorize exposure
  - Collaboration with Air Force historians and Air Force Global Strike Command (AFGSC)
  - Identified 100 current and historical AFSCs related to the missile community
  - N=65,000 personnel in missile community

Cancer Incidence Datasets



Phase 1 Results (review from last year):

- No statistically significant increased risk of cancer or death from cancer
- Based on 55,224 cancer cases
- Phase 2 added Virtual Pooled Registry (VPR) data: 2.7 times more cancer cases than Phase 1

Virtual Pooled Registry
Cancer Linkage System

- Shifted cancer incidence findings

VPR Data Timeline

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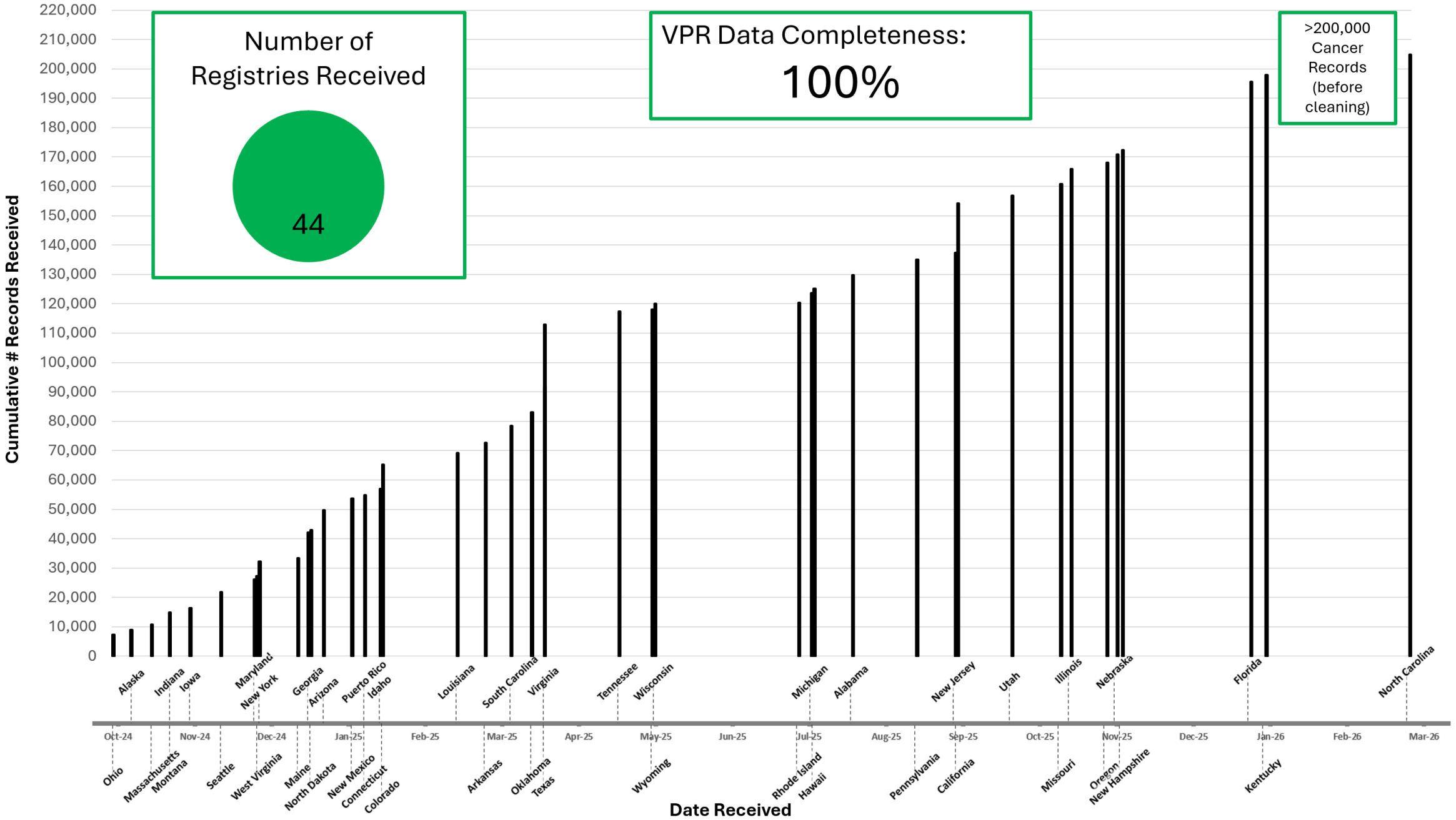
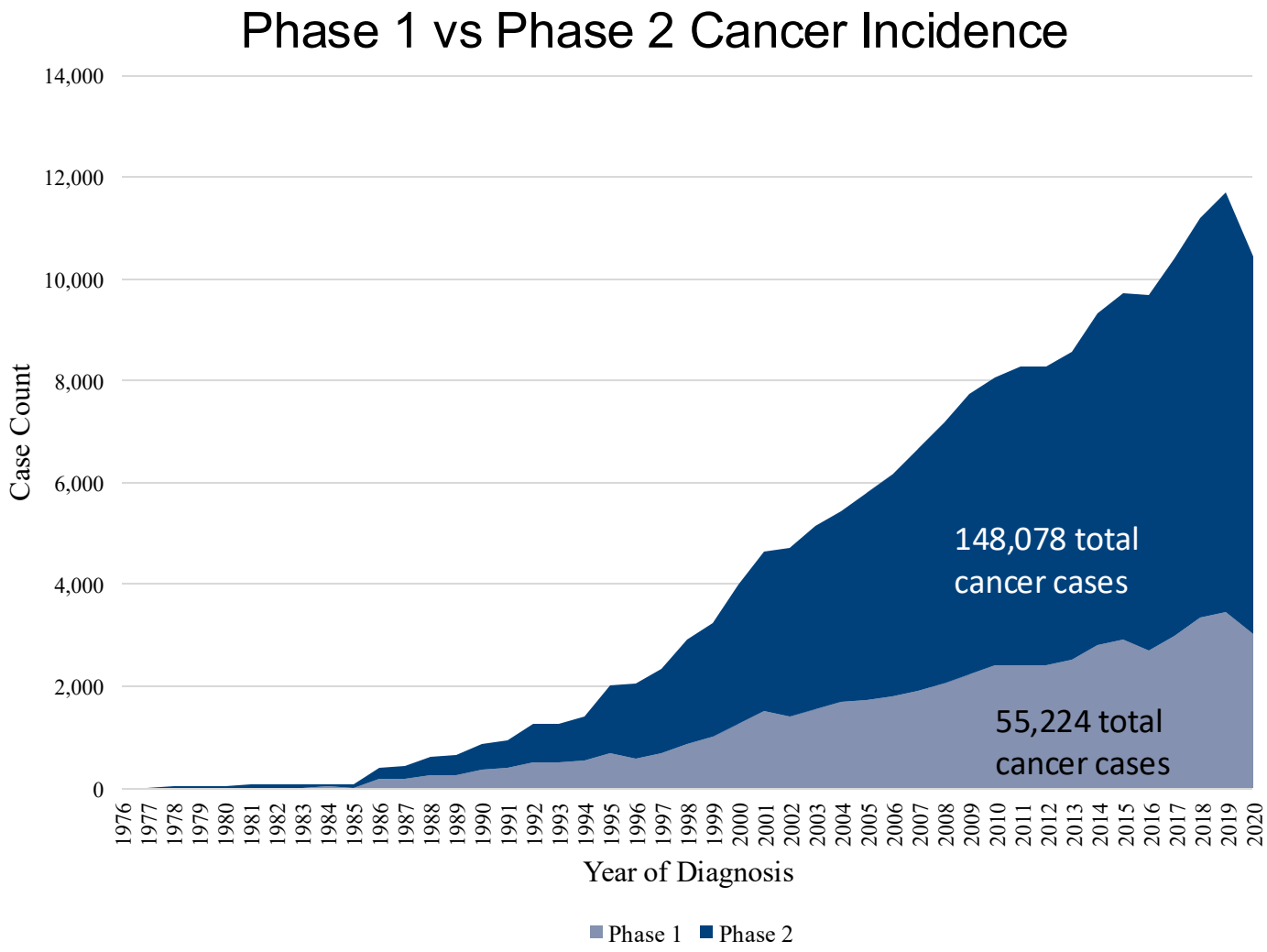


Results

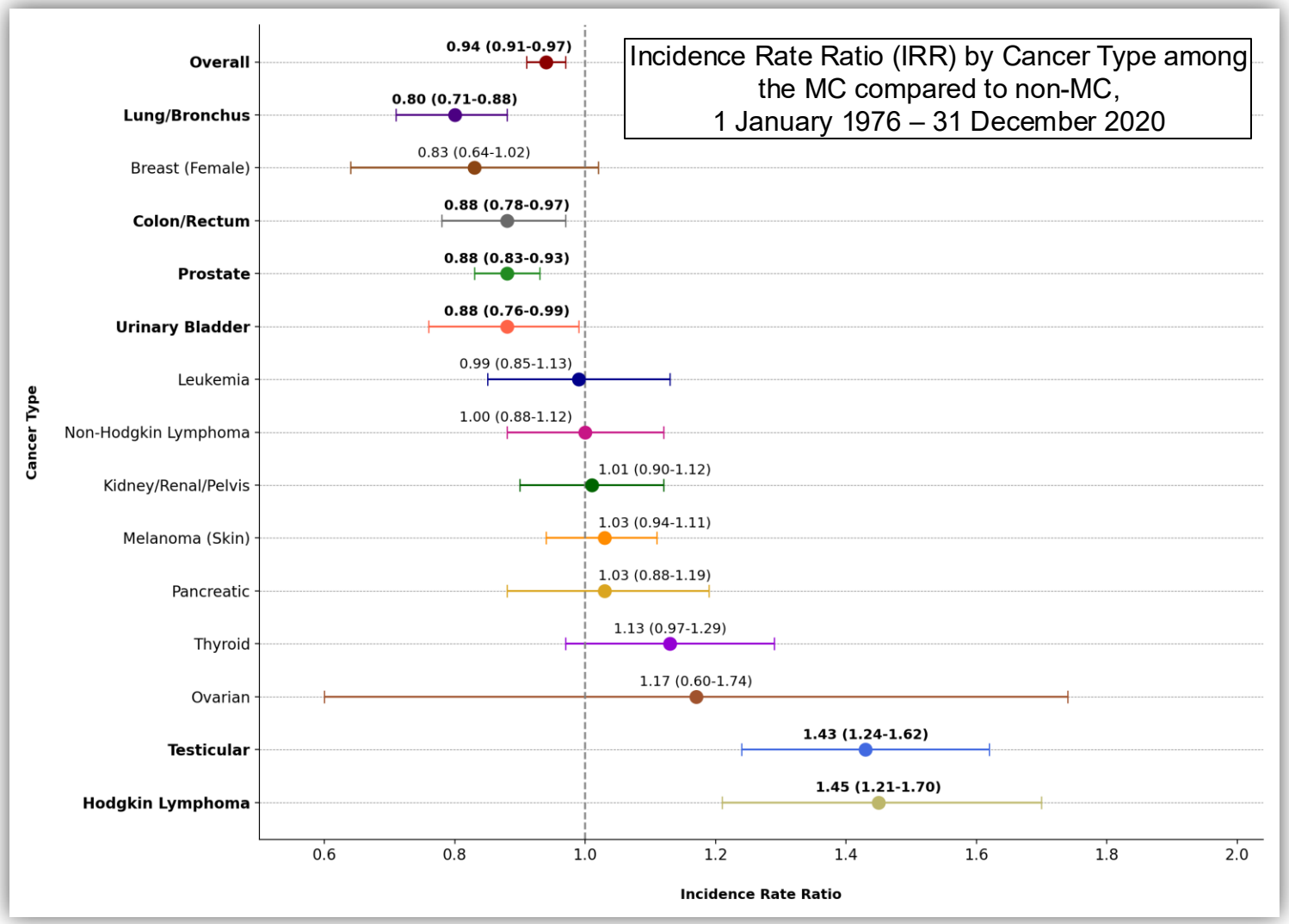
Case Count

Cancer cases (counts(column %)) among missile community and non-missile community, 1 January 1976 – 31 December 2020			
Cancer Type	Missile Community (N=64,735)	Non-Missile Community (N=1,757,033)	Total (N=1,821,768)
All 14 types*	4,942	143,136	148,078
Breast (Female)	109 (2.21%)	7,932 (5.54%)	8,041 (5.43%)
Colon and Rectum	462 (9.35%)	13,729 (9.59%)	14,191 (9.58%)
Hodgkin Lymphoma	67 (1.36%)	1,543 (1.08%)	1,610 (1.09%)
Kidney and Renal Pelvis	320 (6.48%)	7,976 (5.57%)	8,296 (5.60%)
Leukemia	201 (4.07%)	5,457 (3.81%)	5,658 (3.82%)
Lung and Bronchus	582 (11.78%)	18,606 (13.00%)	19,188 (12.96%)
Melanoma of the Skin	546 (11.05%)	14,450 (10.10%)	14,996 (10.13%)
Non-Hodgkin Lymphoma	285 (5.77%)	7,767 (5.43%)	8,052 (5.44%)
Ovarian (Female)	12 (0.24%)	638 (0.45%)	650 (0.44%)
Pancreatic	175 (3.54%)	4,407 (3.08%)	4,582 (3.09%)
Prostate (Male)	1,626 (32.90%)	44,958 (31.41%)	46,584 (31.46%)
Testicular (Male)	111 (2.25%)	2,688 (1.88%)	2,799 (1.89%)
Thyroid	154 (3.12%)	4,543 (3.17%)	4,697 (3.17%)
Urinary Bladder	292 (5.91%)	8,442 (5.90%)	8,734 (5.90%)
*All primary study cancers counted (individual may have more than 1 primary cancer but not the same type).			



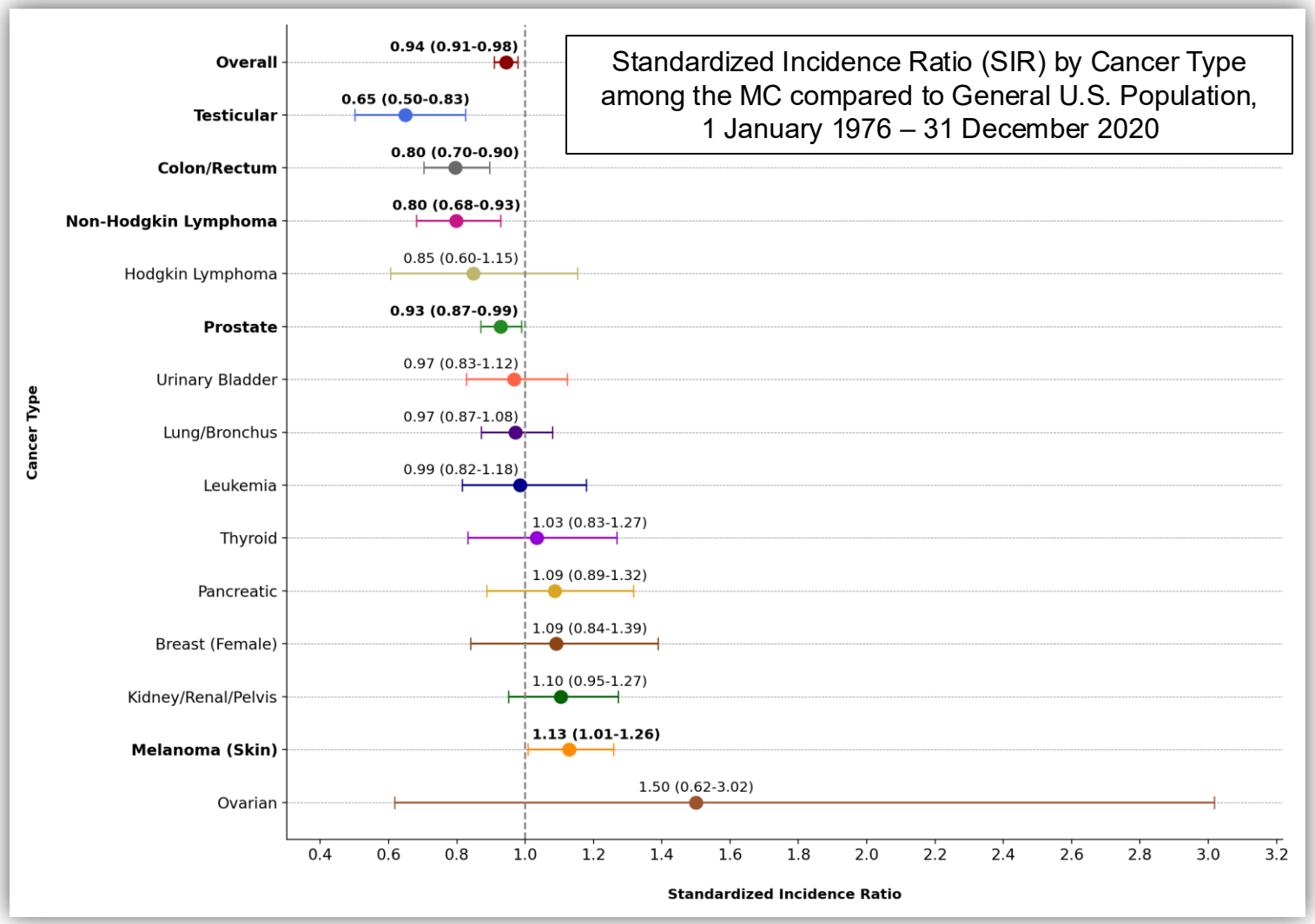
Results – Internal Comparison

- **MC vs non-MC**
  - **Increased incidence:**
    Testicular cancer
    Hodgkin lymphoma
  - **Statistically similar incidence:**
    Female breast cancer
    Leukemia
    Non-Hodgkin lymphoma
    Kidney/Renal pelvis cancer
    Melanoma
    Pancreatic cancer
    Thyroid cancer
    Ovarian cancer
  - **Lower incidence:**
    All 14 cancers overall
    Lung/Bronchus cancer
    Colon/Rectum cancer
    Prostate cancer
    Bladder cancer



Results – External Comparison

- **MC vs General U.S. population**
  - **Increased incidence:**
    Melanoma
  - **Statistically similar incidence:**
    Hodgkin lymphoma
    Bladder cancer
    Lung/Bronchus cancer
    Leukemia
    Thyroid cancer
    Pancreatic cancer
    Female breast cancer
    Kidney/Renal pelvis cancer
    Ovarian cancers
  - **Lower incidence:**
    All 14 cancers overall
    Testicular cancer
    Colon/Rectum cancer
    Non-Hodgkin lymphoma
    Prostate cancer

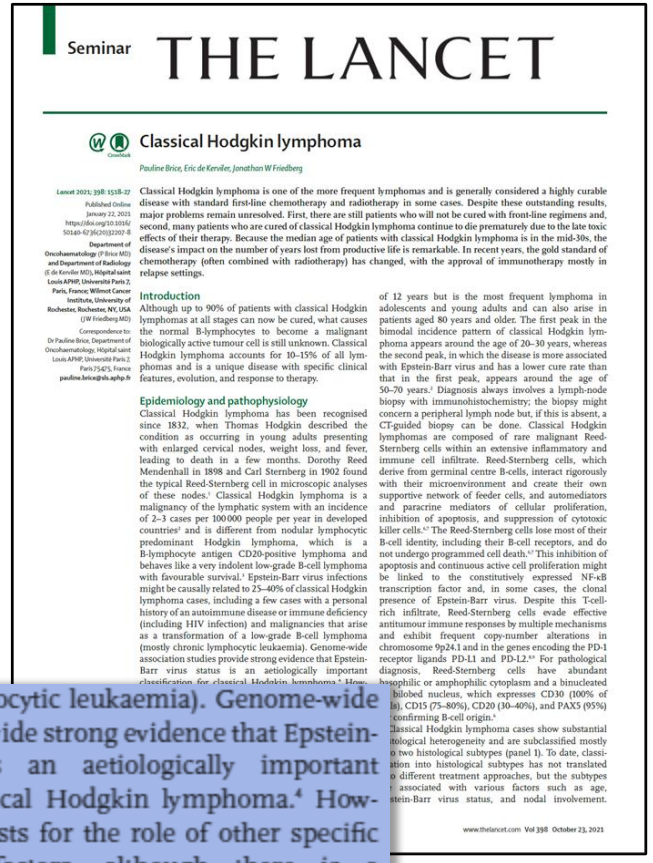


What is Testicular Cancer?

- **Cancer of the male reproductive system**
- **Most common in men aged 20-34 years[1]**
  - 10,000 new cases in the United States annually[1]
  - Highly treatable, 95% 5-year survival rate[1]
- **What causes testicular cancer?**
  - Undescended testes (aka, cryptorchidism) ↑ risk[2]
  - Family history of testicular cancer ↑ risk[2]
  - Prenatal exposure (exposure while fetus is *in utero*) to endocrine disruptors (impacts hormones) ↑ risk[3]
  - Testicular cancer development likely starts *in utero*[4]
- **Do adult occupational exposures increase testicular cancer risk?**
  - Unlikely to have a significant contribution from adult occupational exposure[3]
  - Some cancers have strong associations with occupational exposures, testicular cancer does not[5]

What is Hodgkin Lymphoma?

- **Specific type of cancer of the lymphatic system**
  - Lymphatic system helps maintain fluid balance, filter waste, and fight infection
- **Notably different from non-Hodgkin lymphoma (NHL)**
  - Less common than non-Hodgkin lymphoma[6]
  - More treatable than non-Hodgkin lymphoma, with an 89% cure rate[7]
- **What causes Hodgkin lymphoma?**
  - Infection with the Epstein-Barr virus (up to 40% of cases)[8,10]
  - Family history and genetics[9,10]
- **Do adult occupational exposures increase Hodgkin lymphoma risk?**
  - Unlikely to have a significant contribution from environmental exposures[10]
  - Some cancers have strong associations with occupational exposures, Hodgkin lymphoma does not[5]



Seminar THE LANCET

Classical Hodgkin lymphoma

Pauline Brice, Eric de Kerviler, Jonathon W Friedberg

Classical Hodgkin lymphoma is one of the more frequent lymphomas and is generally considered a highly curable disease with standard first-line chemotherapy and radiotherapy in some cases. Despite these outstanding results, major problems remain unresolved. First, there are still patients who will not be cured with front-line regimens and, second, many patients who are cured of classical Hodgkin lymphoma continue to die prematurely due to the late toxic effects of their therapy. Because the median age of patients with classical Hodgkin lymphoma is in the mid-30s, the disease's impact on the number of years lost from productive life is remarkable. In recent years, the gold standard of chemotherapy (often combined with radiotherapy) has changed, with the approval of immunotherapy mostly in relapse settings.

Introduction

Although up to 90% of patients with classical Hodgkin lymphomas at all stages can now be cured, what causes the normal B-lymphocytes to become a malignant biologically active tumour cell is still unknown. Classical Hodgkin lymphoma accounts for 10–15% of all lymphomas and is a unique disease with specific clinical features, evolution, and response to therapy.

Epidemiology and pathophysiology

Classical Hodgkin lymphoma has been recognised since 1832, when Thomas Hodgkin described the condition as occurring in young adults presenting with enlarged cervical nodes, weight loss, and fever, leading to death in a few months. Dorothy Reed Mendenhall in 1898 and Carl Sternberg in 1902 found the typical Reed-Sternberg cell in microscopic analyses of these nodes.[1] Classical Hodgkin lymphoma is a malignancy of the lymphatic system with an incidence of 2–3 cases per 100 000 people per year in developed countries[2] and is different from nodular lymphocyte predominant Hodgkin lymphoma, which is a B-lymphocyte antigen CD20-positive lymphoma and behaves like a very indolent low-grade B-cell lymphoma with favourable survival.[3] Epstein-Barr virus infections might be causally related to 25–40% of classical Hodgkin lymphoma cases, including a few cases with a personal history of an autoimmune disease or immune deficiency (including HIV infection) and malignancies that arise as a transformation of a low-grade B-cell lymphoma (mostly chronic lymphocytic leukaemia). Genome-wide association studies provide strong evidence that Epstein-Barr virus status is an aetiologically important classification for classical Hodgkin lymphoma.[4] However, little evidence exists for the role of other specific environmental risk factors, although there is a distinctive pattern of incidence rates and risk profiles by age, race or ethnicity, sex, and economic levels.[1] Some

of 12 years but is the most frequent lymphoma in adolescents and young adults and can also arise in patients aged 80 years and older. The first peak in the bimodal incidence pattern of classical Hodgkin lymphoma appears around the age of 20–30 years, whereas the second peak, in which the disease is more associated with Epstein-Barr virus and has a lower cure rate than that in the first peak, appears around the age of 50–70 years.[1] Diagnosis always involves a lymph-node biopsy with immunohistochemistry; the biopsy might concern a peripheral lymph node but, if this is absent, a CT-guided biopsy can be done. Classical Hodgkin lymphomas are composed of rare malignant Reed-Sternberg cells within an extensive inflammatory and immune cell infiltrate. Reed-Sternberg cells, which derive from germinal centre B-cells, interact rigorously with their microenvironment and create their own supportive network of feeder cells, and automediators and paracrine mediators of cellular proliferation, inhibition of apoptosis, and suppression of cytotoxic killer cells.[4,5] The Reed-Sternberg cells lose most of their B-cell identity, including their B-cell receptors, and do not undergo programmed cell death.[6,7] This inhibition of apoptosis and continuous active cell proliferation might be linked to the constitutively expressed NF-κB transcription factor and, in some cases, the clonal presence of Epstein-Barr virus. Despite this T-cell-rich infiltrate, Reed-Sternberg cells evade effective antitumour immune responses by multiple mechanisms and exhibit frequent copy-number alterations in chromosome 9p24.1 and in the genes encoding the PD-1 receptor ligands PD-L1 and PD-L2.[8,9] For pathological diagnosis, Reed-Sternberg cells have abundant basophilic or amphophilic cytoplasm and a binucleated biloped nucleus, which expresses CD30 (100% of ls), CD15 (75–80%), CD20 (30–40%), and PAX5 (95%) confirming B-cell origin.[1]

lassical Hodgkin lymphoma cases show substantial tological heterogeneity and are subclassified mostly o two histological subtypes (panel 1). To date, classi- ation into histological subtypes has not translated o different treatment approaches, but the subtypes associated with various factors such as age, tein-Barr virus status, and nodal involvement.

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What is Melanoma?

- **Specific type of cancer of the skin**
  - Starts in the cells that give skin its color (called melanocytes)
- **What causes melanoma?**
  - Ultraviolet (UV) radiation exposure[11]
  - Skin type and other genetic factors[11]
- **Do adult occupational exposures increase melanoma risk?**
  - Studies on workplace exposure to UV radiation show mixed results.
    - Outdoor workers have lower rates of melanoma than indoor workers[7]
    - Occasional sunburns (vs steady sun exposure) ↑ risk[12,13]
    - Recreational exposure to UV radiation likely plays a larger role[13,14]
  - Some cancers have strong associations with occupational exposures, melanoma does not[5]
  - Circadian rhythm disruptions increase risk of certain cancers (breast, prostate, colorectal), limited but emerging evidence for melanoma[15]
  - Increased melanoma incidence in specific DAF[16] and military populations[17,18]

Summary and Way Ahead

Summary

- With MC vs non-MC (the Internal Comparison) there was found an increased incidence of testicular cancer and Hodgkin lymphoma, however:
  - Neither cancer is typically associated with adult occupational exposures, or likely to have significant contribution from adult occupational exposures.
- With MC vs US population (the External Comparison) there was found an increased incidence of melanoma, however:
  - This increased incidence of melanoma is consistent with other cancer epidemiology studies among specific DAF and DOW populations;
  - Non-UV occupational exposure is unlikely to contribute significantly to melanoma.

Way Ahead

- **Continue Epidemiology Review –** Work with external partners to focus in on specific jobs, time periods and bases with increased cancer incidence, as feasible
- **Stakeholder Engagement**
  - Continued Townhalls with the Missile Community
  - VA Coordination
    - Military Environmental Exposure Sub-Council briefings
    - Missile Community roster successfully transferred to VA for ongoing monitoring/updates

- **Website for public information/questions:** [Missile Community Cancer Study (af.mil)]

Questions?

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