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Agent Orange Exposure & Risk of Pancreatic Carcinogenesis

M. Usman Ahmad, MD, Postdoctoral Research Fellow, Stanford University
Nate Fillmore, PhD, Assistant Professor, Harvard Medical School
Albert Lin, MD, Professor, Medical Oncology at VA Palo Alto & Stanford University
George Poultsides, MD, MS, Professor, Department of Surgery, Stanford University

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History & Background

1962-1971

- U.S. military sprayed herbicides over Vietnam as part of military strategy
  - 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), & 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were the main constituents of **Agent Orange (AO)**
- Multiple herbicides were deployed including Agent Pink, Agent Green, Agent Purple, Agent Orange, Agent Orange II, Agent White, and Agent Blue
  - All containing 2,4,5-T and TCDD

Exposure of Service Members

- Estimated 2.6-4.3 million Americans served during the Vietnam War
- High risk groups of service members include
  - Air Force personnel & Army Chemical Corps.

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Calculated AO Risk Models

Calculated Models of Exposure

- Exposure Opportunity Index Model
  - Concluded that ground troops may have also been exposed and included in epidemiologic studies
- AgDRIFT® (Agricultural DRIFT) Model
  - Ground troops could be exposed with direct deposition, post-application transfer from foliage but not from soil or dust

Total Exposed

- Total Exposed (TE) = Air Force + Army Chemical Corp + (Ground Troops*X)
- X is unknown and difficult to estimate given a lack of documentation

Table I
Estimated Number of Marines Near Areas Where Agent Orange Was Used

Within kilometers of sprayed area	Within days of spraying mission	Estimated no. of marines
.5	1	5,900
	7	7,600
	14	9,100
	28	16,100
1.5	1	16,500
	7	21,500
	14	25,800
	28	30,100
2.5	1	17,400
	7	23,900
	14	29,900
	28	39,400

AO/TCDD Exposure Risk

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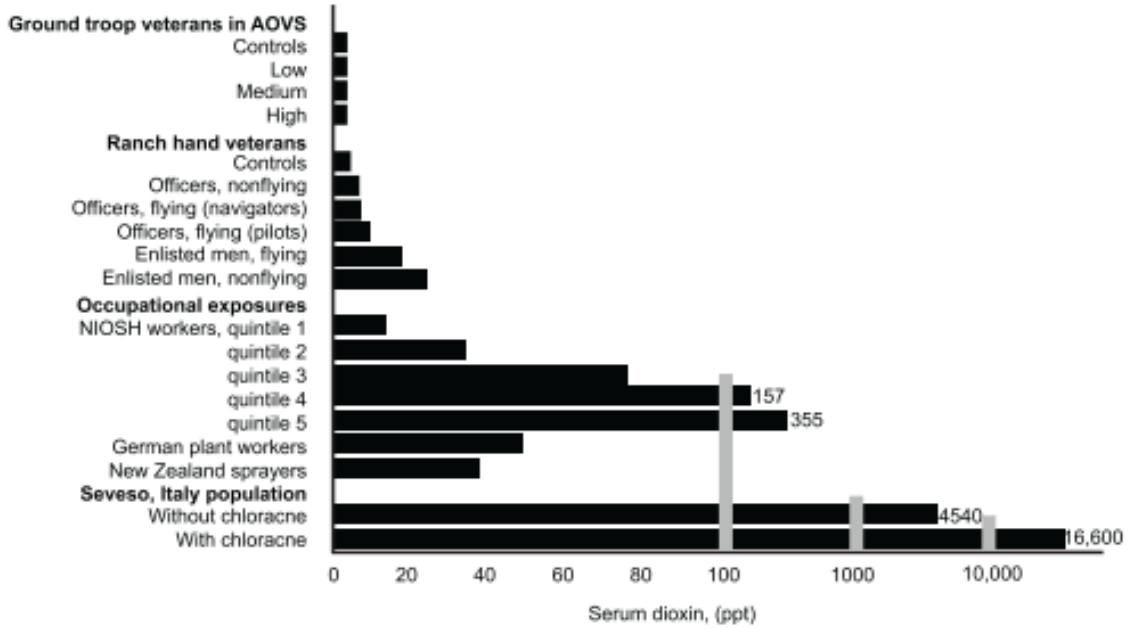
- TCDD Levels
  - Levels of this chemical were used to determine the level of exposure and comparability of evidence
  - The level of exposure of Veterans included in a government study was lower than those measured from occupational exposure (Fig 1.)
  - The half-life of this chemical is approx. 7 years
  - However, a single study evaluating sampling fat found:
    - Prostate Cancer patients had dioxin toxic equivalency (TEQ) was elevated in AO exposed vs unexposed patients (22.3 vs 15 pg/g, p<0.001) at the time of cancer surgery

Figure 1



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Summary of Exposure to AO

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- Many Veterans may have been exposed to AO or similar chemical herbicides
- At this time, self-reporting is used as a proxy from AO exposure regardless of official reporting and records
- Although serum levels of dioxin are limited in usability, fat dioxin may be a proxy that may confirm exposure in patients

Summary of Known Cancer Risk

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Evidence Supports Carcinogenesis	Limited Evidence Supports Carcinogenesis	Evidence Insufficient for Carcinogenesis
• Soft tissue sarcoma • Non-Hodgkin's Lymphoma • Chronic Lymphocytic Leukemia • Hodgkin's Lymphoma • MGUS	• Laryngeal Cancer • Lung, bronchus, or trachea • Prostate Cancer • Bladder Cancer • Multiple Myeloma • AL amyloidosis	• Oral, nasal, or pharyngeal cancer • Esophageal Cancer • Stomach Cancer • Colorectal Cancer • Hepatobiliary Cancer • **Pancreatic Cancer** • Small Intestine, Bone, Skin, Breast, Gynecologic, Testicular, Renal, Brain, Thyroid, & Leukemia

National Academies of Sciences, Engineering, and M. *Veterans and Agent Orange*; National Academies Press: Washington, D.C., 2018; Vol. 11; ISBN 978-0-309-47716-1.

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Overall Studies for Cancer Risk

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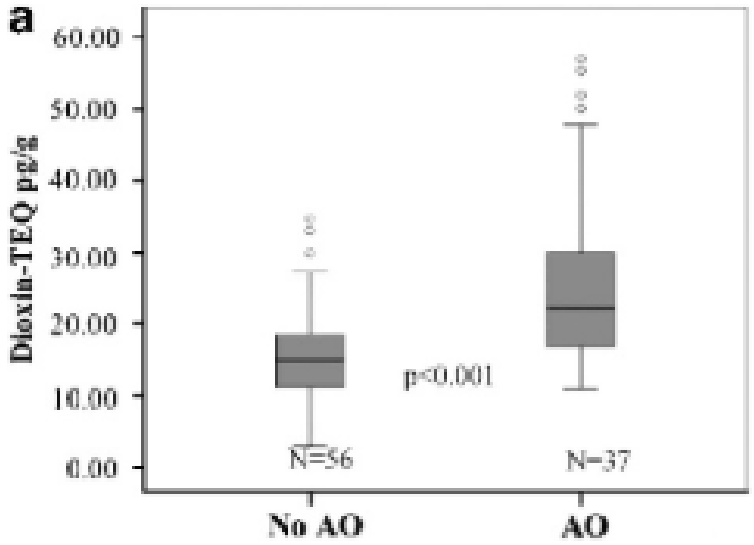
- Validated study designs have included long term follow-up in occupational exposure for accepted classifications of association such as sarcoma
- Self-reported exposure to AO appears valid when compared to fat harvesting from patients and measuring dioxin-TEQ in prostate cancer patients.



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Global Study Results

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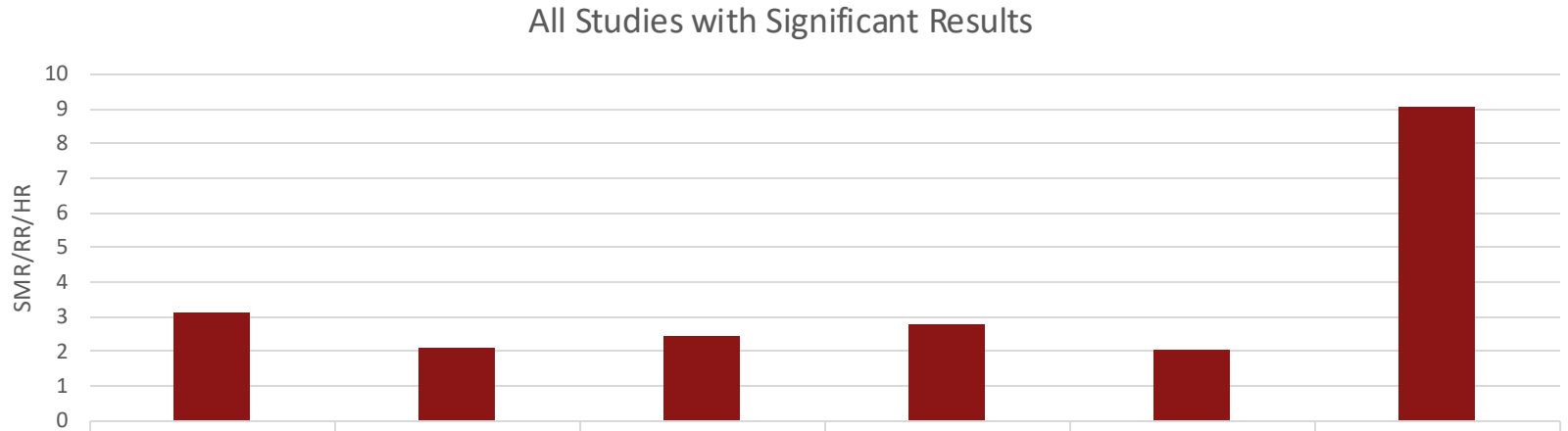

AO?	N/A	Self-report	N/A	N/A	N/A	N/A
Occupation	All	All	Nurses	Nurses	Nurses	All
Race	All	All	All	All	All	Black
Gender	Male	Male	Female	Female	Female	Male
Population	Veterans	Veterans	Veterans	Veterans	Veterans	Veterans
Total (N)	43969	114562	9911	6973	8237	1729
PDAC (N)	26	510	25	10	35	6
Journal	Aus Govt	J of Pre Med & Pub Hea	Ann of Epi	J of Occ & Env Med	Am J of Epi	J of Occ & Envir Med
Year	2005	2013	2008	1995	2014	1995
Author	Aus Govt	Yi	Cypel	Dalager	Kang	Visintainer
Country	AUS	Korea	USA			

Overall, most significant studies did not control for AO exposure and various other confounding variables. However, populations at significant risk with exposure may include Australian Veterans, Korean Veterans self-reporting exposure, Black American Veterans, and American Nurse Veterans (over multiple studies).

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U.S. Study Results

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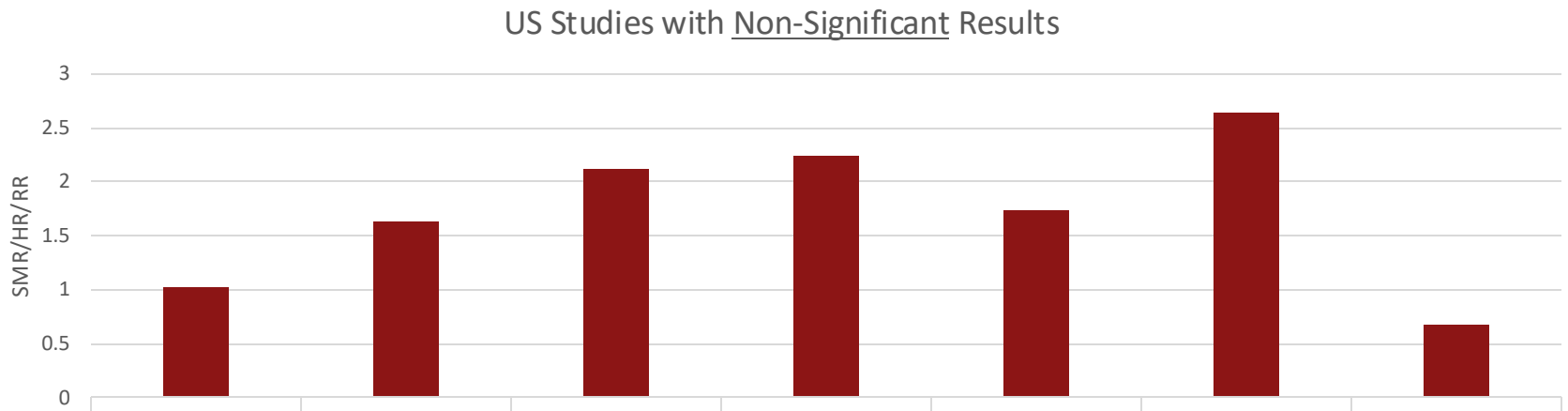

AO?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gender	Male	Male	Female	Female	Female	Female	Male
Population	Veterans	Veterans	Veterans	Veterans	Veterans	Veterans	Veterans
Total (N)	18313	50920	6973	9911	12104	9900	6864
PDAC (N)	10	100	33	12	50	8	9
Journal	Arc Int Med	J of Occ Med	Ann of Epi	J of Occ & Env Med	Am J of Epi	Am J of Epi	J of Occ & Env Med
Year	2004	1988	2008	1995	2014	1991	1995
Author	Boehmer	Breslin	Cypel	Dalager	Kang	Thomas	Visintainer

Overall, all non-significant studies did not control for AO exposure and various other confounding variables. However, 5/7 studies show increased risk for Veterans when compared to control populations

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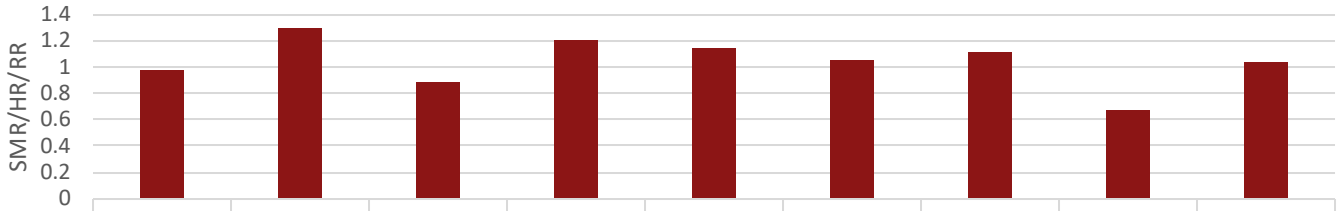
Non U.S Study Results

Non-US Studies with Non Significant Results



AO?	Estimated	N/A	N/A	N/A	N/A	Estimated	Estimated	N/A	N/A
Occupation	All	RAAF	Navy	Army	All	All	All	All	All
Population	Workers	Veterans	Veterans	Veterans	Veterans	Veterans	Veterans	Veterans	Workers
Gender	All	Male	Male	Male	Male	Male	Male	Male	All
Total (N)	26976	4570	13538	41084	59192	96126	180251	3394	8036
PDAC (N)	47	12	14	60	86	433	184	5	54
Journal	Am J of Epi	Aus Govt				J of Pre Med & Pub Hea	Can	BMJ Open	Occ & Env Med
Year	1997	2005				2013	2014	2013	2015
Author	Kogevinas	Aus Govt				Yi		McBride	Coggon
Country	All	AUS				Korea		New Zealand	UK

Overall, many studies did not control for AO exposure and various other confounding variables. However, 6/9 results show increased risk when compared to control populations although they are not statistically significant

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Summary of Previous Studies

- Prior studies of Vietnam veterans from US and Australian cohorts reported excess pancreatic cancer, however, later studies from New Zealand and Korean veterans did not.
- Government reports have not addressed the most recent studies for US Nurse Veterans and pancreatic cancer which show significant associations for Black Veterans and pancreatic cancer.
- Most studies have not analyzed confounding factors beyond age, race, and gender e.g. smoking, AO exposure, etc.

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Limitations of Previous Studies

- Excess death due to violence, poisoning, and early death e.g. < 35 years of age > pancreatic cancer occurs 60s-70s normally
- Lack of reporting of confounding variables or those included in the analysis
- Lack of specificity of AO exposure
- Overall, many studies assessing PDAC are of modest quality given limitations of data and non-specific.
- The largest sample size of PDAC in a given study is less than 600 cases.

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Overall Design

- Population: Veterans with and without pancreatic cancer
- Exposure: Agent Orange (AO) Exposure
- Confounding Variables: Smoking, Alcohol, Diabetes, Age, Race, Gender, Metformin, Aspirin, Statins, NSAIDs, Warfarin, Occupational Hazards, & Genes
- Methods: Nationalized datasets from the Veterans Affairs Data Warehouse including: Veterans Affairs Central Cancer Registry (VACCR), Agent Orange Registry (AOR), National Patient Care Database (NPCD), and VA Drug Accountability or Pharmacy Benefit Manager Database, Million Veterans Project (MVP)
- Multivariable analysis of association with AO including confounding variables. Rather than a case-control study, we will use multivariable regression across a large sample.
- Outcomes: Odds ratio of risk of pancreatic cancer with AO exposure. We may also detect protective risk factors with concomitant use of common drugs in this population that have some proven benefit in the general population.

Cohort Overview

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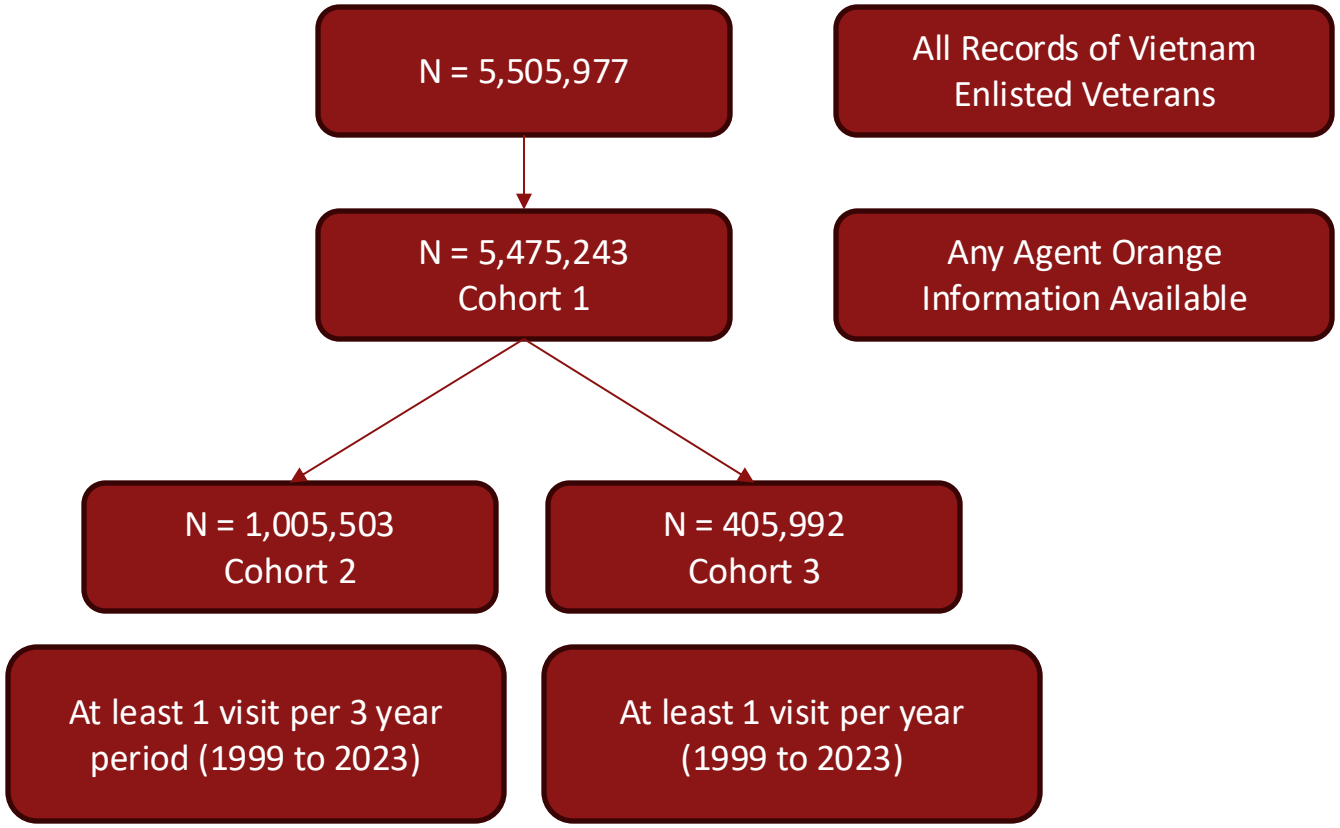

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Costs/Benefits to Using Cohorts

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- All information and follow up data may not be accurate in the general cohort
- Co-variates such as smoking, diabetes, and other factors may not be accurate in the general cohort
- If sampled incorrectly, then the smaller cohort may not represent the general population and provide the incorrect result

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Agent Orange Exposure Identification

- The disability file was used to find the value of the Agent Orange exposure for each patient.
- AO exposure was defined as any veteran who was flagged in the disability data under “Agent Orange Exposure”.
- These data are validated in the disability database to determine a veteran’s claim, which are defined clinically using the PACT Act.10,25 AO exposure is based on
  - (1) having a health condition associated with AO per VHA (updated over time) and
  - (2) having served in a location with exposure to AO.

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Overall Cohort Demographics

Table 1: Baseline Characteristics	Overall cohort	1 visit per 3 years	1 visit per year
	N = 5,505,977	N = 1,005,503	N = 405,992
Agent Orange	1,203,125 (22%)	189,157 (19%)	84,195 (21%)
Male Gender	5,395,969 (98%)	981,571 (98%)	394,364 (97%)
Black	541,711 (9.8%)	171,508 (17%)	72,806 (18%)
Hispanic	190,490 (3.5%)	44,764 (4.5%)	19,314 (4.8%)
Last Branch			
Army	2,388,200 (45%)	517,515 (52%)	218,725 (54%)
Navy	891,734 (17%)	150,674 (15%)	60,254 (15%)
Air Force	739,385 (14%)	126,060 (13%)	52,546 (13%)
Marines	360,650 (6.8%)	74,881 (7.5%)	28,885 (7%)
All Other/Unknown	898,287 (17%)	129,864 (13%)	43,039 (11%)
Alcohol Disorder	901,011 (16%)	333,745 (33%)	134,655 (33%)
Smoking	1,562,124 (28%)	510,677 (51%)	205,911 (51%)
Diabetes	1,771,232 (32%)	520,367 (52%)	228,637 (56%)
Obesity	1,279,169 (23%)	427,095 (42%)	185,394 (46%)
Any Metformin History	1,102,686 (20%)	351,627 (35%)	153,102 (38%)
Any Warfarin History	328,404 (6.0%)	140,102 (14%)	66,722 (16%)
Any Statin History	2,735,760 (50%)	787,169 (78%)	325,510 (80%)
Pancreatic Cancer	12,870 (0.2%)	4,795 (0.5%)	2,328 (0.6%)

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Pancreatic Cancer Rates in Cohorts & AO Association

Cohort Name	AO Status	Cancer	OR (CI), p-value
Cohort 1	AO	0.25%	**1.087 (0.88-0.96), p<0.0001**
n=5,475,243	No AO	0.23%	
Cohort 2	AO	0.49%	1.034 (0.96-1.11), p=0.36
n=1,005,503	No AO	0.47%	
Cohort 3	AO	0.61%	1.078 (0.98-1.19), p=0.13
n=405,992	No AO	0.56%	

*Chi-Square Test

Regression Results on Risk and Pancreatic Cancer

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Table 3: Logisitic Regression on Risk Variables and Pancreatic Cancer Incidence

Cohort	n=5,474,131				n=1,005,503				n=405,992			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
Variable	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value	Odds Ratio	P-Value
Agent Orange	1.087	**<0.001**	1.007	0.725	1.034	0.355	1.026	0.480	1.078	0.134	1.084	0.110
Male Gender	1.323	**<0.001**	1.203	**0.011**	1.194	0.086	1.105	0.335	1.096	0.480	1.016	0.903
Black Race	1.936	**<0.001**	1.490	**<0.001**	1.490	**<0.001**	1.431	**<0.001**	1.402	**<0.001**	1.359	**<0.001**
Hispanic Ethnicity	1.161	**0.001**	1.051	0.271	1.062	0.379	1.111	0.128	0.926	0.449	0.959	0.683
Alcohol Disorder	1.956	**<0.001**	1.328	**<0.001**	1.104	**0.001**	0.982	0.576	1.049	0.272	0.971	0.527
Smoking	2.423	**<0.001**	1.788	**<0.001**	1.301	**<0.001**	1.323	**<0.001**	1.161	**<0.001**	1.188	**<0.001**
Diabetes	2.487	**<0.001**	1.531	**<0.001**	1.355	**<0.001**	1.282	**<0.001**	1.295	**<0.001**	1.218	**0.001**
Obesity	1.714	**<0.001**	1.028	0.186	0.946	0.058	0.883	**<0.001**	0.929	0.079	0.877	**0.004**
Metformin	2.566	**<0.001**	1.448	**<0.001**	1.360	**<0.001**	1.334	**<0.001**	1.327	**<0.001**	1.362	**<0.001**
Warfarin	2.219	**<0.001**	1.521	**<0.001**	1.119	**0.005**	1.152	**<0.001**	1.001	0.982	1.039	0.498
Statin	2.200	**<0.001**	1.148	**<0.001**	0.752	**<0.001**	0.615	**<0.001**	0.717	**<0.001**	0.602	**<0.001**

Cancer Outcomes & AO: Cohort 1

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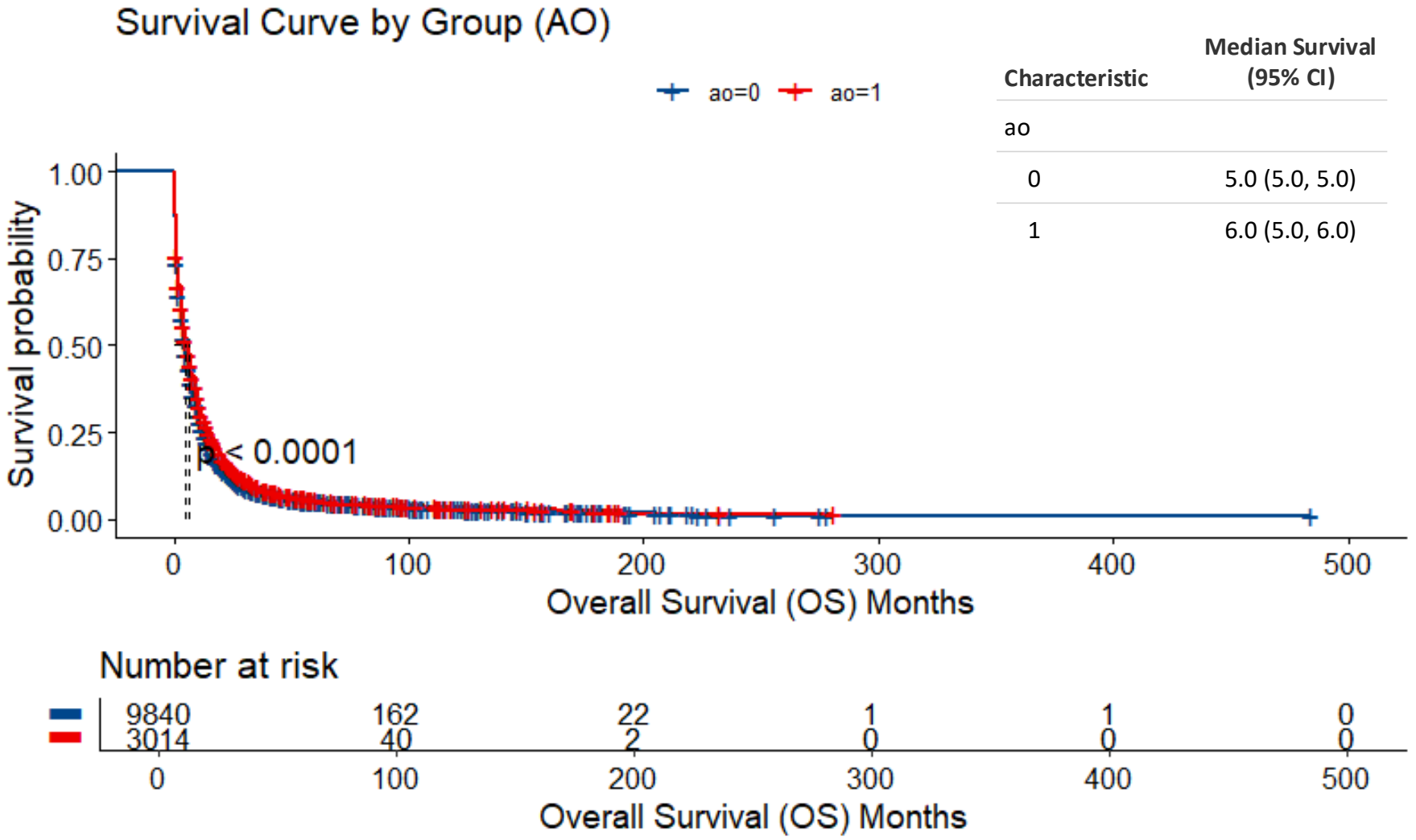

Characteristic	Median Survival (95% CI)
ao	
0	5.0 (5.0, 5.0)
1	6.0 (5.0, 6.0)

Cancer Outcomes & AO: Cohort 2

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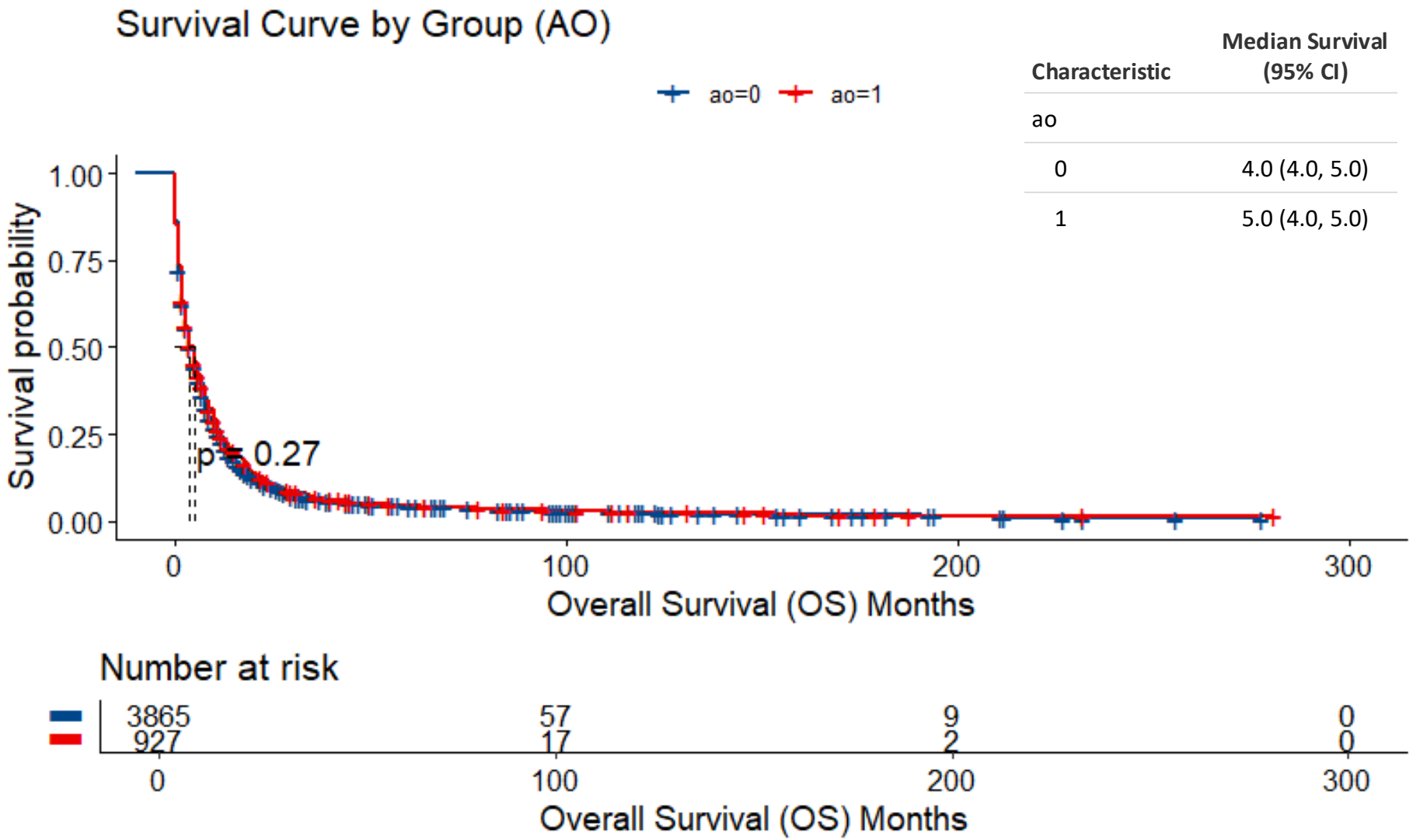

Characteristic	Median Survival (95% CI)
ao	
0	4.0 (4.0, 5.0)
1	5.0 (4.0, 5.0)

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Cancer Outcomes & AO: Cohort 3

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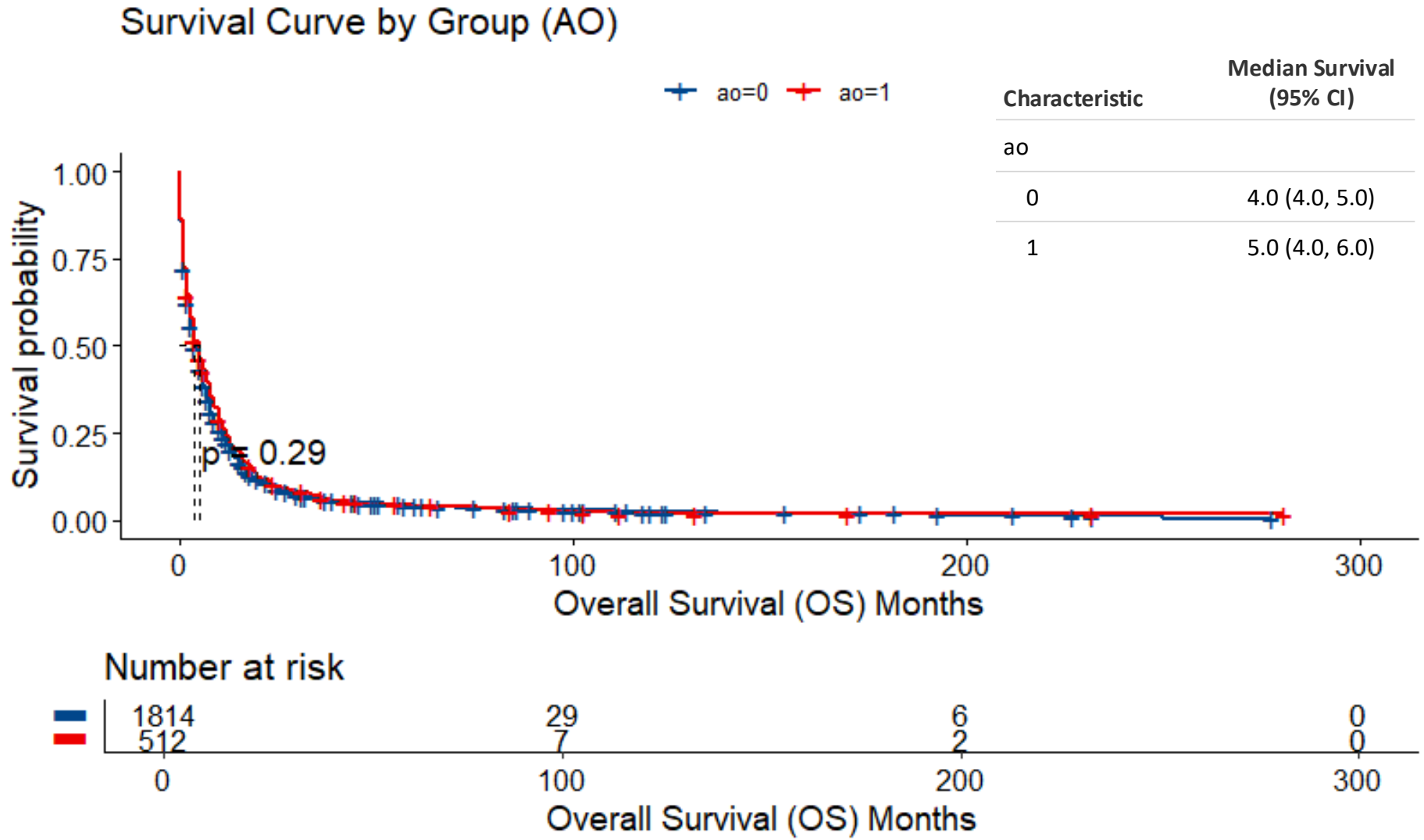

Characteristic	Median Survival (95% CI)
ao	
0	4.0 (4.0, 5.0)
1	5.0 (4.0, 6.0)

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Cancer Outcomes & AO

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- Overall, there does not appear to be a consistent risk of pancreatic cancer associated with AO exposure
- Smoking and Diabetes are associated with pancreatic cancer
- Black Race may also be associated with pancreatic cancer

Agent Orange Exposure & Risk of Pancreatic Carcinogenesis

Ahmad MU, Fillmore N, Lin A, Poultsides GA

- Questions?