

An aerial photograph of a city, likely Seattle, showing a dense urban area with numerous buildings, streets, and green spaces. A river is visible in the lower-left corner, flowing through the city. The image is partially obscured by a white curved shape on the right side.

How Does Lung Cancer Develop in Never-Smokers?

Looking for Answers in Genomic Sequencing

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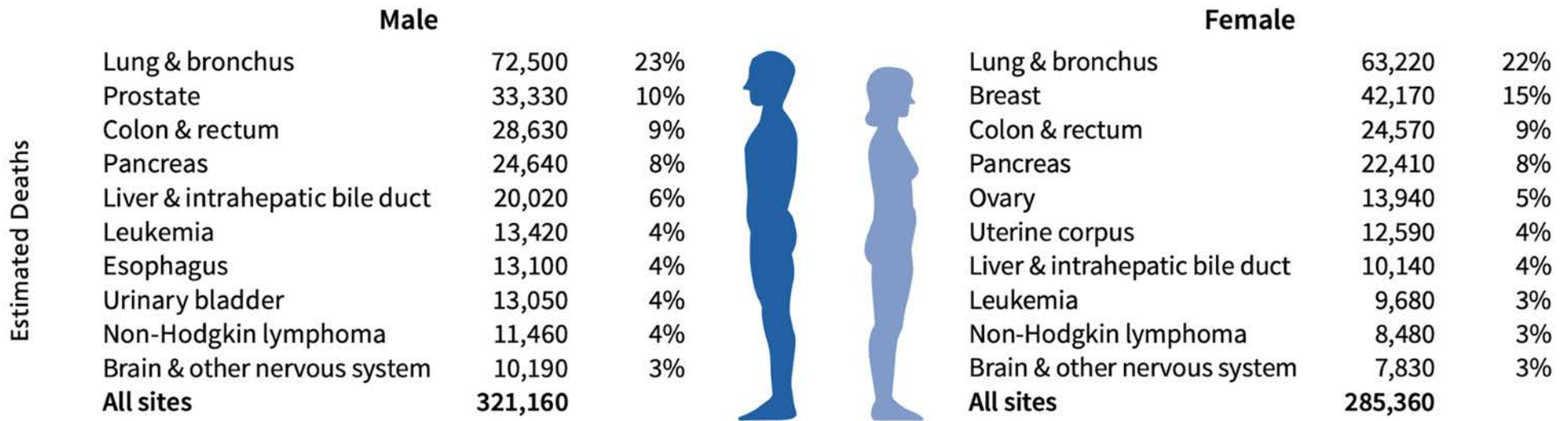
I have no relevant financial relationships in the last 24 months to disclose.



Population:
30,995



Lung cancer is the leading cause of cancer deaths in men and women



135,700 deaths per year! Much greater than the population of Morgantown, WV!

Risk factors for cancer can be intrinsic (genetic) or extrinsic (environmental) factors

Intrinsic:



e.g. *BRCA1* mutations

Extrinsic:



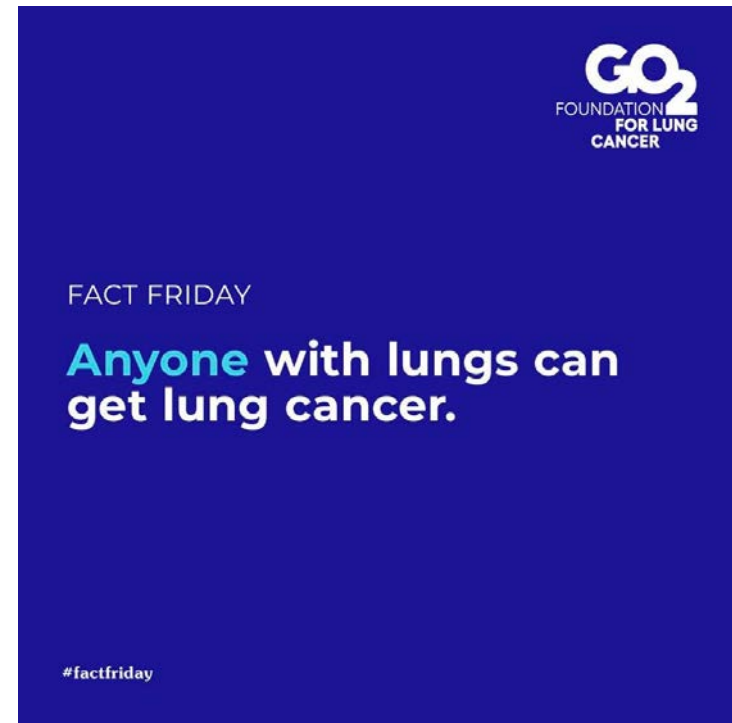
e.g. smoking exposure

1986



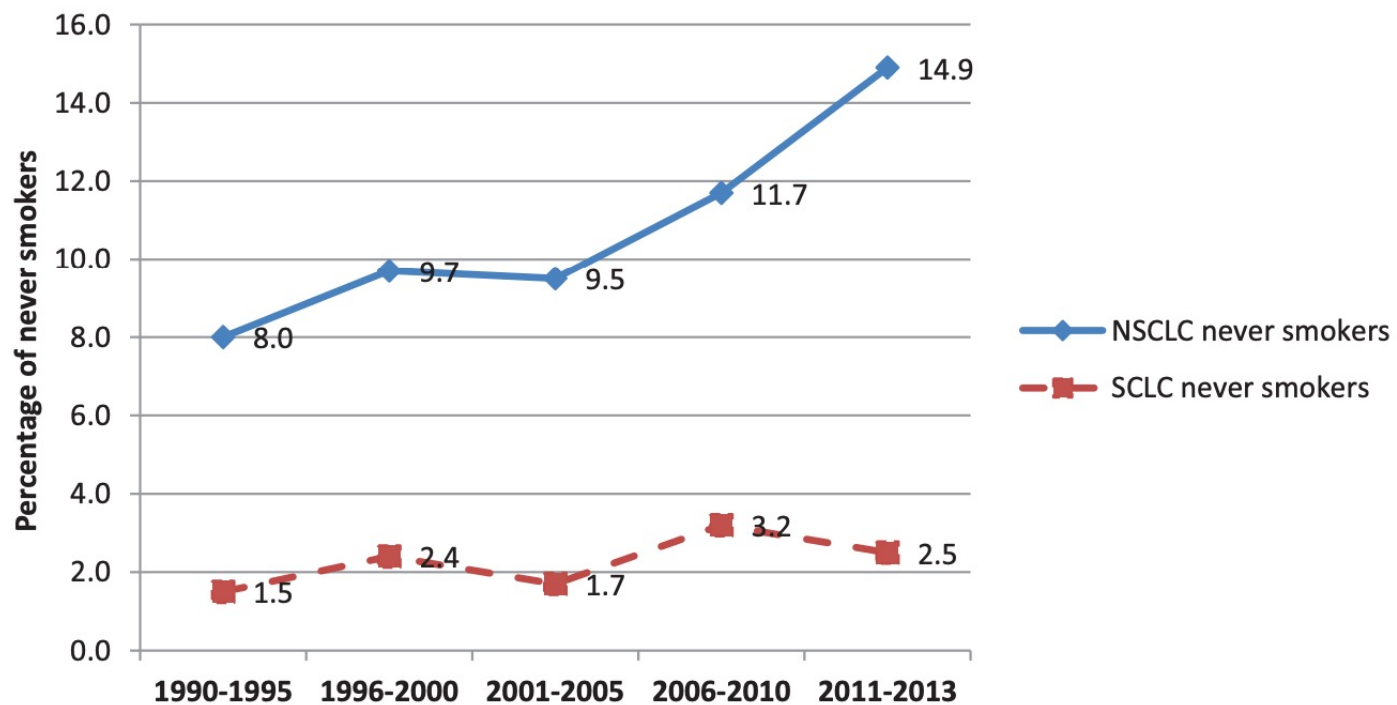
American Lung Association

2019



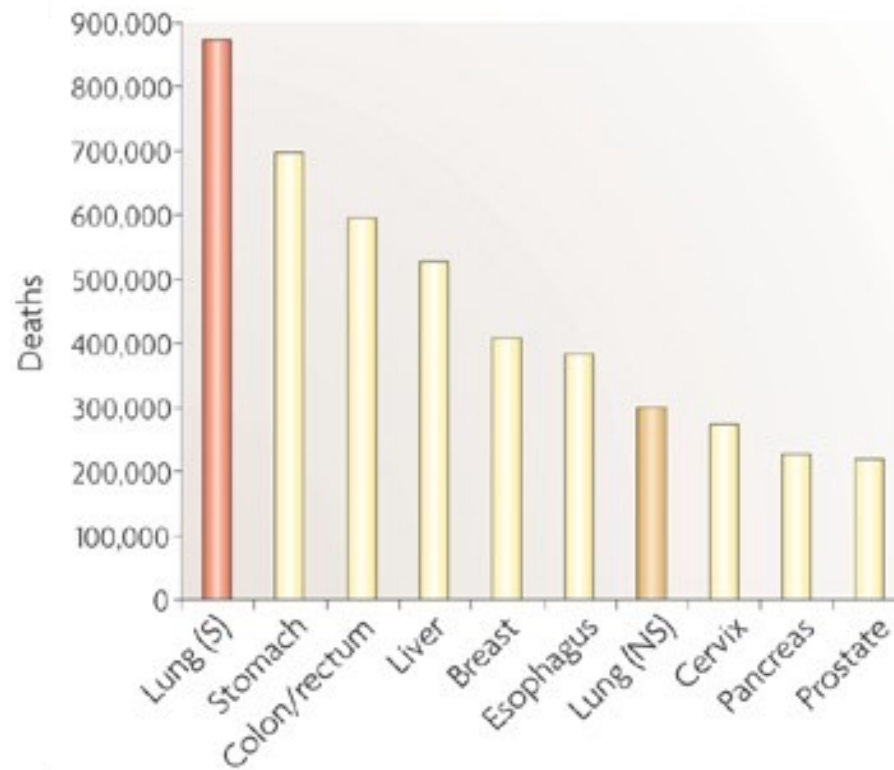
GO2 foundation for lung cancer

A growing proportion of lung cancer is in “never-smokers”



Pelosof et al., JNCI 2017

Lung cancer in never-smokers is the 7th leading cause of cancer deaths

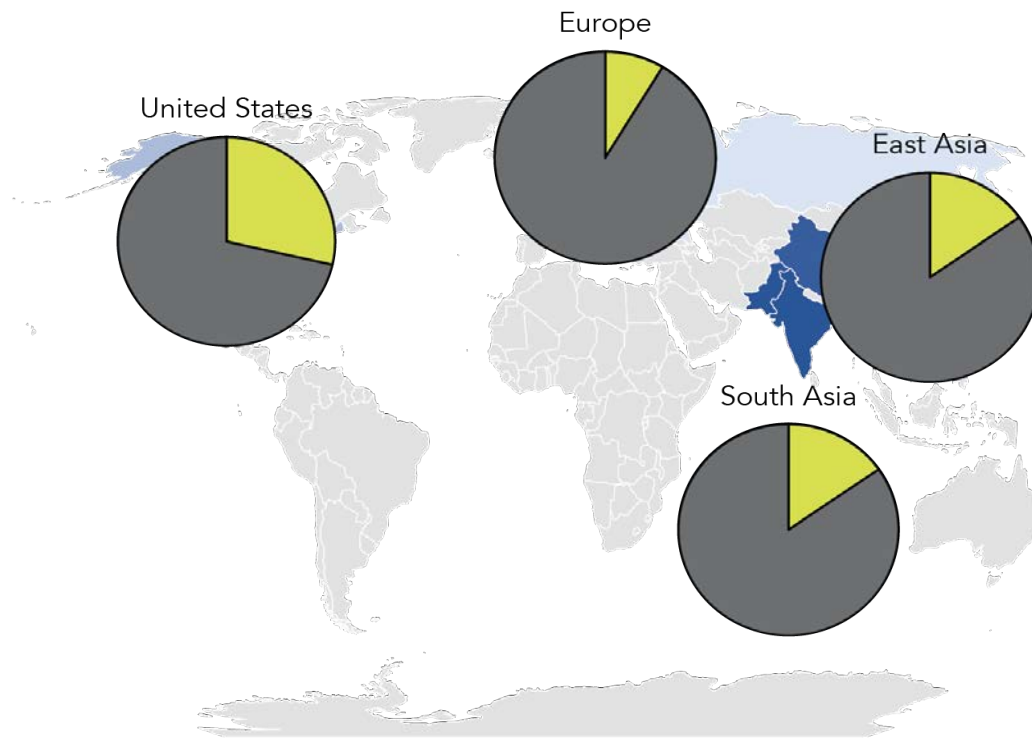


Sun et al., Nat Rev Cancer 2007

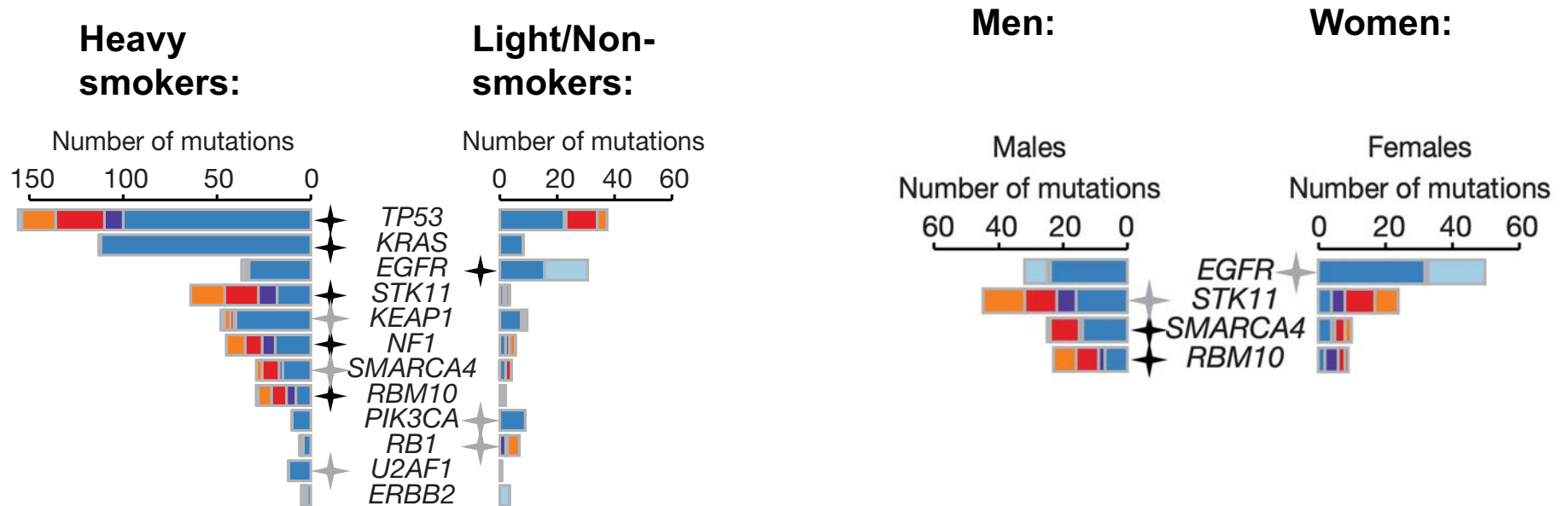
Women account for the majority of lung cancer cases in never-smokers

■ Men
■ Women

↑ Increasing proportion of LCNS



The mutational landscape of lung cancer is affected by smoking status, gender



Motivating questions

- Are there new mutations in lung cancers from never-smokers that could be targeted with cancer therapies?
- Can the mutational profile of the cancers themselves, tell us something about the intrinsic or extrinsic genetic risk factors?
 - Define mutational signatures
 - Demonstrate how smoking alters mutational signatures
 - Illustrate how intrinsic risk factors may also play a role

Challenge: The majority of lung cancers sequenced to date are from smokers.

Motivating questions

- Are there new mutations in lung cancers from never-smokers that could be targeted with cancer therapies?
- Can the mutational profile of the cancers themselves, tell us something about the intrinsic or extrinsic genetic risk factors?
 - Define mutational signatures
 - Demonstrate how smoking alters mutational signatures

Challenge: The majority of lung cancers sequenced to date are from smokers.

The Women's Health Initiative (WHI) lung cancer cohort



Increased cohort size

Post-menopausal women

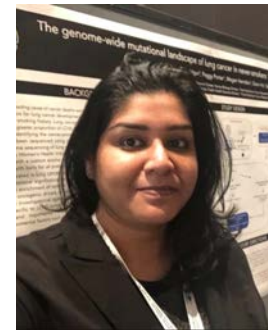
Understudied lung cancer population



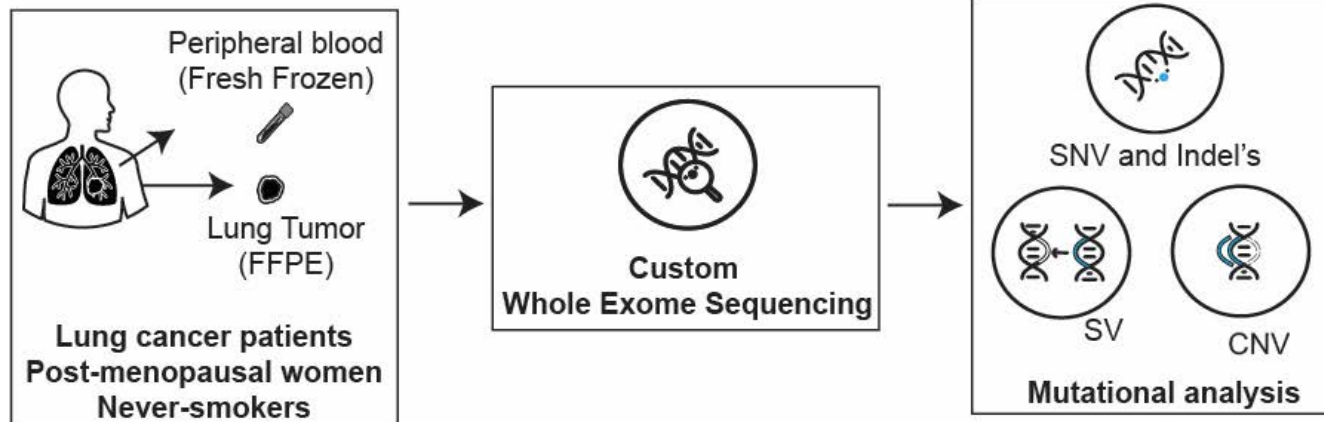
Dr. Garnet Anderson

Extensive metadata

History of second-hand smoke exposure, occupational exposure and demographics



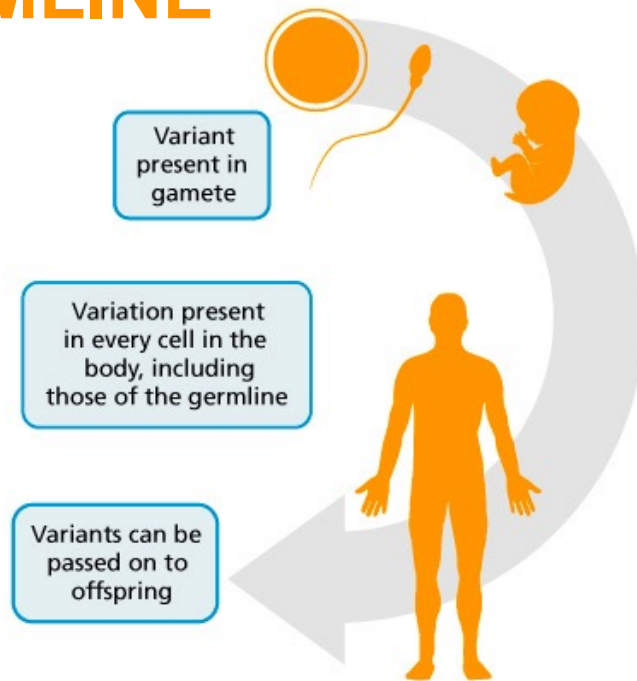
Dr. Sitapriya Moorthi



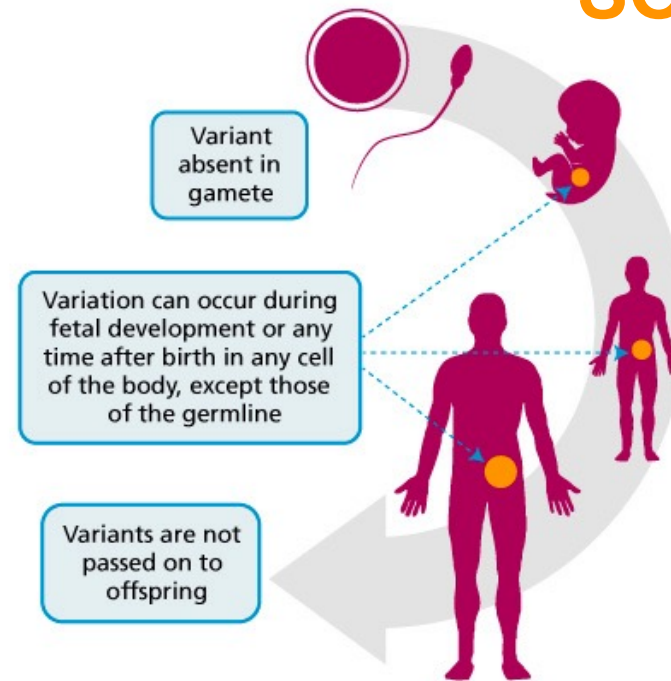
Never-smoker	57
Heavy smoker	18
Total	75

“Germline” vs. “somatic” mutations

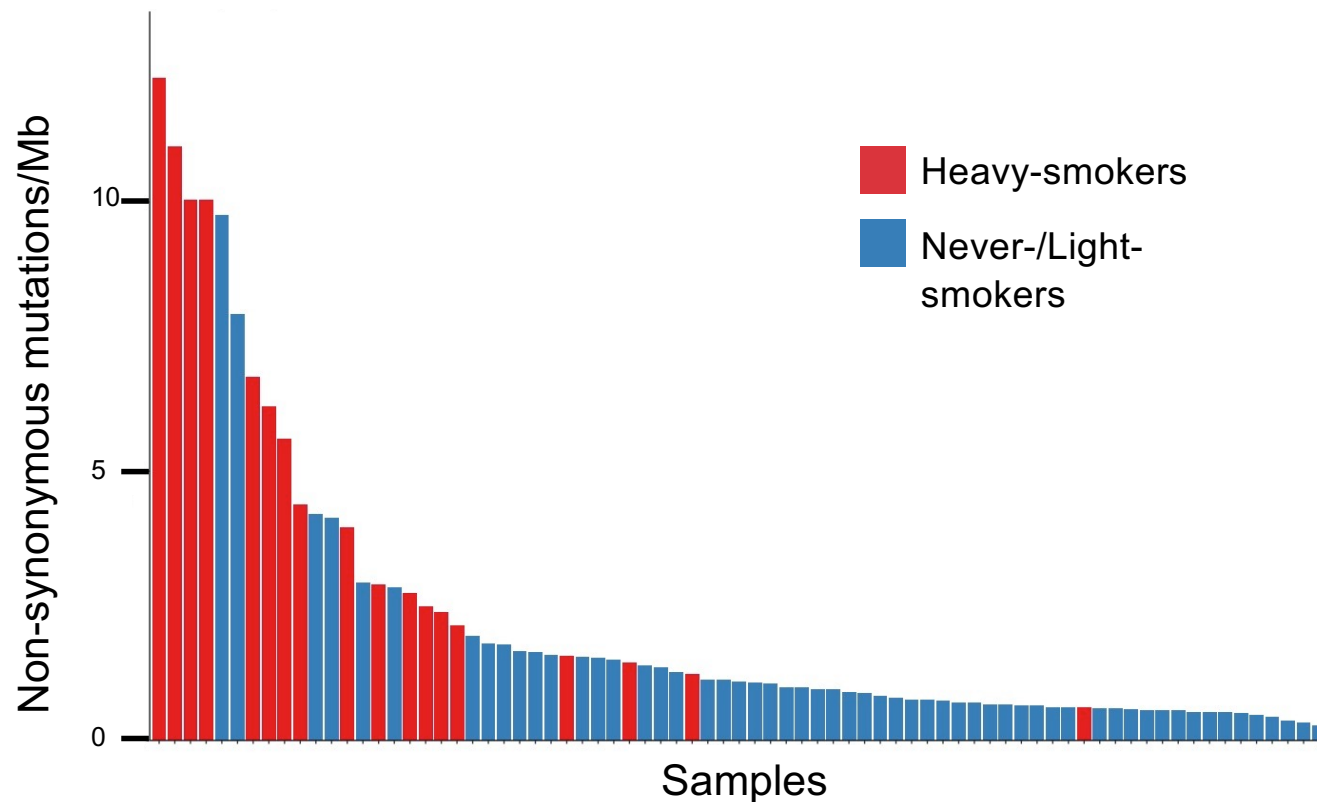
GERMLINE



SOMATIC



Increased mutational burden in lung cancers from smokers



Never-smokers have lower mutational burden.

Identifying somatic mutations in tumors

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80 257-9961	Cartagena Avith	1500 North St	617 442-9780	
17 566-1282	Cartagena Lydia	19 Sweet Hill Ave	617 323-7639	
17 364-5188	Carte Nicholas	301 Ames St	617 576-1061	
361-0380	Carte Nicholas	301 Ames St	617 576-1061	
17 566-4548	Carte Nicholas	301 Ames St	617 576-1061	
17 428-8248	Carte Nicholas	301 Ames St	617 576-1061	
17 445-5116	Carte Nicholas	301 Ames St	617 576-1061	
17 822-2982	Carte Nicholas	301 Ames St	617 576-1061	
17 827-9712	Carte Nicholas	301 Ames St	617 576-1061	
17 569-2698	Carte Nicholas	301 Ames St	617 576-1061	
17 667-5190	Carte Nicholas	301 Ames St	617 576-1061	
17 569-1417	Carte Nicholas	301 Ames St	617 576-1061	
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17 825-9195	Carte Nicholas	301 Ames St	617 576-1061	
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17 670-2078	Carte Nicholas	301 Ames St	617 576-1061	
17 523-9001	Carte Nicholas	301 Ames St	617 576-1061	
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17 879-0030	Carte Nicholas	301 Ames St	617 576-1061	
17 436-1513	Carte Nicholas	301 Ames St	617 576-1061	
17 569-8119	Carte Nicholas	301 Ames St	617 576-1061	
800 569-8782	Carte Nicholas	301 Ames St	617 576-1061	

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80 257-9961	Cartagena Avith	1500 North St	617 442-9780	
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17 364-5188	Carte Nicholas	301 Ames St	617 576-1061	
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17 569-8119	Carte Nicholas	301 Ames St	617 576-1061	
800 569-8782	Carte Nicholas	301 Ames St	617 576-1061	

Normal tissue

Tumor

ACTGGCATCGATCGAGAGACCTAGCGTGTATAGCCGGTAGGAATGGC...

...like finding typos in 200 volumes of the phone book



What is a “mutational signature”?

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800 257-9901	Cartagena Avith 11 Pleasant St 02118.....	617 442-9780	Franklin & Anne 200 Mt Auburn St 02118.....	617 325-6781	Nick 21 Currier Ave 02118.....	617 257-5222
17 566-1282	B Hill 02118.....	617 361-5253	Fred 45 Rowland St 02118.....	617 524-3878	Nick & Debbie 100 Morris Hill Newton 02459.....	617 527-0490
17 364-5188	Jessica 30 Rowland St 02118.....	617 281-6152	Fred 68 Rowland St 02118.....	617 698-1443	Norman G 30 Chesham St 02118.....	617 822-1203
361-0380	Lucilla 120 Rowland St 02118.....	617 491-5621	G & R 100 Rowland St 02118.....	617 436-8906	P 34 Commonwealth St 02118.....	617 422-4754
17 566-4546	M 19 Rowland St 02118.....	617 323-9711	G T 27 Franklin St 02118.....	617 623-7121	P E 101 E South St 02118.....	617 266-8213
17 428-8248	Melvin 100 Green Cove 02118.....	617 576-1861	Geoff 25 Franklin St 02118.....	617 825-6322	P L 68 Haskings St 02118.....	617 422-9170
17 445-5116	Carte Nicholas 14 Quimper Boston 02118.....	617 695-6996	Gene S 123 West Hill Rd 02118.....	617 325-3215	P R 41 Beacon Ave 02118.....	617 983-8692
17 822-7982	Carte Thomas J Sr & Claire 17 Pavilion Rd 02118.....	617 338-8219	George 120 South Ave 02118.....	617 567-9548	Paul B Constance 114 Acorn Ave W 02118.....	617 325-2036
17 627-3712	Thomas & Kathleen 30 Tremont St 02118.....	617 698-6163	Carter Halliday Associate 100 Central Ave 02118.....	617 456-1689	Paul E 201 E South St 02118.....	617 266-6546
17 569-2698	Carte A Inc 02118.....	617 327-2257	Carter Harry F 100 Irving Ave W 02118.....	617 325-5465	Paul M 27 Union St 02118.....	617 787-2115
17 647-5190	A 11 South St 02118.....	617 442-1219	Carter HD&G Co Inc 145 Sumner Ave 02118.....	617 542-7887	Carter Pile Drilling Inc 17 Forest St Franklin 02118.....	781 235-8488
17 569-1417	A 200 Beacon St 02118.....	617 492-1374	Horace 141 Walnut Av Rowbury 02118.....	617 442-5307	Carter Prudence 40 Franklin Waterfront 02118.....	617 393-3782
17 828-9110	A M 305 Main St 02118.....	617 266-7153	Howard Jr 25 Nebra Drive 02118.....	617 445-5532	Prudence 40 Franklin Waterfront 02118.....	617 926-7063
17 296-1593	Alice 108 Main St 02118.....	617 425-0193	J 15 Chestnut St 02118.....	617 232-7990	Reginald 100 Franklin Waterfront 02118.....	617 541-2043
17 676-2078	Alice 40 Market Cambridge 02118.....	617 965-2711	J 250 Harvard St 02118.....	617 738-8483	Renee & Andrew 100 Franklin St 02118.....	617 726-3765
17 623-9001	Andrew F 20 West Av 02118.....	617 625-7623	J 770 Via Pines West Rowbury 02118.....	617 323-5574	Carter Rice David Robby Dutton Publishing 143 Main Wilmington 01897.....	800 638-1671
17 296-4725	Carte Anne MD 1301 Beacon Ave 02118.....	617 739-1022	Carter J M 100 Cambridge St 02118.....	617 735-8787	Carl See Industrial Prod 413 Main Wilmington Tel Free State P & N.....	500 619-7447
17 542-1521	Carte Athens 377 Beacon Boston 02118.....	617 536-6329	Carter J M Ornamental Ironworks Call.....	617 464-1040	Carl See Printing 413 Main Wilmington Tel Free State P & N.....	800 648-7447
17 364-5232	Carte Barbara L MD 100 Beacon St 02118.....	617 296-6911	Carter J Veal Co 60 Westwood St 02118.....	617 436-5353	Headquarters 413 Main Wilmington 01897 Call.....	978 988-7447
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17 739-2662	Bernard J 172 Cambridge St 02118.....	617 567-3430	James 100 Cambridge St 02118.....	617 492-1214	Richard 100 Cambridge St 02118.....	617 987-0836
17 879-8038	Bibbiah 25 Winslow Dr 02118.....	617 298-8713	Jays L 14 Rowbury Rd 02118.....	617 361-0773	Richard A Jr 18 Sumner St 02118.....	617 546-7293
17 436-1513	Blank 30 Mt Vernon Ave 02118.....	617 367-9931	John 124 Beacon St 02118.....	617 968-8435	Carter Richard A MD 170 Cambridge St 02118.....	617 267-0710
17 569-4319	Carte Broadcasting Co 10 Park St 02118.....	617 423-8210	Jeffrey 41 Beacon Ave 02118.....	617 426-5994	Carter Richard K 100 Mount St 02118.....	617 268-0448
800 569-8782	Carte & Burgess Consultants Inc 10 Park St 02118.....	617 225-0200	John 124 Beacon St 02118.....	617 957-2163	Robert L 170 Beacon St 02118.....	617 986-1535
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	C 200 Harvard St 02118.....	617 569-1545	John 124 Beacon St 02118.....	617 282-1235	Roy 48 Concord Ave 02118.....	617 491-6115
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	C 200 Harvard St 02118.....	617 554-9536	John 124 Beacon St 02118.....	617 282-1235		

e.g. in one gene

What is a “mutational signature”?

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800 257-9901	Cartagena Aveth	11 Pleasant St 02114	617 442-9780	Franklin S 204 Essex St 02116	617 325-6781	Franklin & Anne	211 Portland Ave 02114	617 690-5222		
117 566-1282	Cartagena B	11 Pleasant St 02114	617 361-5253	Fred 45 Rowland St 02114	617 524-3078	G & R 100 Adams St 02114	617 522-0490	Nick & Debbie	100 Essex St 02114	617 690-5222
117 364-5188	Cartagena Lucilla	111 Vermont St 02114	617 491-5621	Frederic 18 Rowland St 02114	617 690-1843	G & R 100 Adams St 02114	617 522-0490	Norman G	100 Essex St 02114	617 690-5222
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117 445-5116	Cartagena P	111 Vermont St 02114	617 690-6163	Carter Halliday Associate	617 456-1680	George 120 North St 02114	617 567-9548	P 24 Chestnut St 02114	617 822-1103	617 822-1103
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117 623-9001	Cartagena Z	111 Vermont St 02114	617 690-6163	Carter Halliday Associate	617 456-1680	George 120 North St 02114	617 567-9548	P 24 Chestnut St 02114	617 822-1103	617 822-1103
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117 879-0030	Cartagena AF	111 Vermont St 02114	617 690-6163	Carter Halliday Associate	617 456-1680	George 120 North St 02114	617 567-9548	P 24 Chestnut St 02114	617 822-1103	617 822-1103
117 430-1513	Cartagena AG	111 Vermont St 02114	617 690-6163	Carter Halliday Associate	617 456-1680	George 120 North St 02114	617 567-9548	P 24 Chestnut St 02114	617 822-1103	617 822-1103
117 569-4119	Cartagena AH	111 Vermont St 02114	617 690-6163	Carter Halliday Associate	617 456-1680	George 120 North St 02114	617 567-9548	P 24 Chestnut St 02114	617 822-1103	617 822-1103
800 569-8782	Cartagena AI	111 Vermont St 02114	617 690-6163	Carter Halliday Associate	617 456-1680	George 120 North St 02114	617 567-9548	P 24 Chestnut St 02114	617 822-1103	617 822-1103

Many genes...

...seemingly unrelated

What is a “mutational signature”?

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17 566-1282	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 364-5188	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
361-0380	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 566-4546	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 428-8240	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 445-5116	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 822-2982	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 427-3712	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 569-2698	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 647-5190	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
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17 296-1599	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 676-2078	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 633-9001	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 296-4725	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 542-1521	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 364-5232	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 541-5649	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 739-2662	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 879-0038	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 436-1513	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
17 569-4119	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222
800 569-8782	Cartagena Aveth	617 361-5253	Franklin & Anne	617 356-7811	Cartier S F	100 Washington Ave 02115	617 257-5222

Same type of mutation!



Evidence of the *cause*

Second-hand smoke?

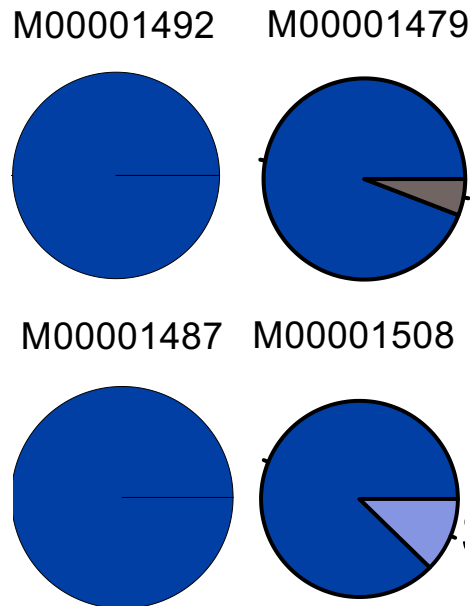
Aging?

Radon?

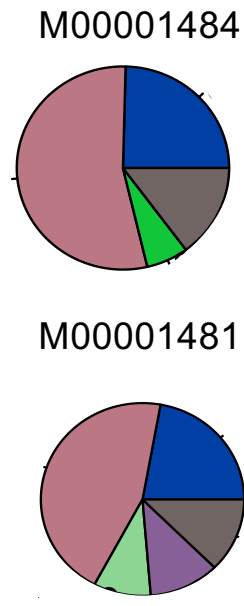
Something else?

Smokers and never-smokers have different mutational signatures

Never-smokers:



Smokers:



Conclusion

- Anyone with lungs can get lung cancer
- Differing mutational signatures in smokers and never-smokers point to different underlying etiology
- Future direction: etiology of lung cancer in younger vs. older patients may also differ
 - Lack of chromosomal translocations in post-menopausal women

Acknowledgements



Berger Lab:

Shriya Kamapurkar

April Lo

Maria McSharry

Sitapriya Moorthi, Ph.D.

Phoebe Parrish

Amanda Riley



Collaborators:

Garnet Anderson, Ph.D.

Amy Paguirigan, Ph.D.

Gavin Ha, Ph.D.

