

Cancer Occurrence in Offsite Neighborhoods Near the Santa Susana Field Laboratory

Thomas Mack, M.D., M.P.H.
Keck School of Medicine
University of Southern California

Reasons for Concern

- Intensive testing of rocket fuels
 - Usage of solvents, chemicals, metals, radionuclides
 - Presumed carcinogen contamination
 - Lymphomas and lung cancers among workers
-
- History of accidents, spills and releases
 - Possible dispersion offsite by air and water
-
- Safety conditions relaxed, inadequate monitoring
 - History of secrecy and non-responsiveness

Reasons for Scientific skepticism

- Lack of any clear risk found by previous searches

Previous searches were Inconclusive

Study	Periods	Locations	Cancers	Conclusions
Perkins-Wright	1978-82	5 LA Tracts	11 Sites	Single Tract Bladder 1.5 83-7
	1983-87			Overall: Inconclusive
Coye-Goldman	1973-82	Aggregated Tracts by County	14 Sites aggregated	Bladder 1.3 83-88 LA tracts
	1983-88			Lung 1.1 88-89 VEN Tracts
	1988-89			Suspect Confounding
Nasseri	1988-95	Aggregated VEN Co Tracts	12 Sites aggregated	No positive findings
Morgenstern	1988-95	Aggregated LA, VEN Blocks in 3 belts by Distance	9 Sites aggregated	Lung 1.1 Middle Belt 88-95
	1996-02			Melanoma 1.2 Middle Belt 96-02 Thyroid ? Proximity effect Aerodigestive? Proximity effect

Problems with Previous searches

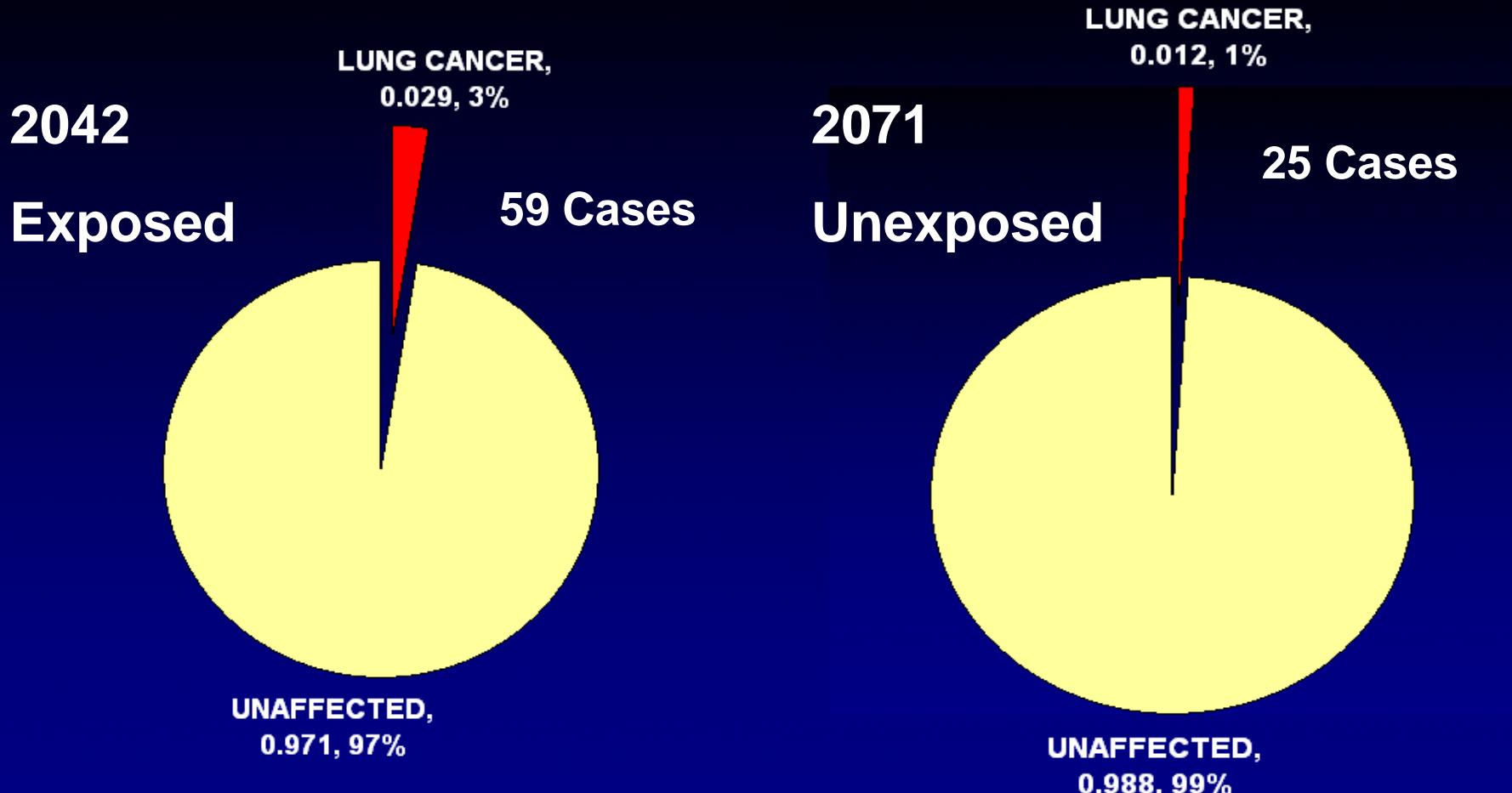
Study	Problems
Perkins-Wright	Multiple comparisons without adjustment Weak associations Bias: response to cluster report Confounded by Race and Social Class
Coye-Goldman	Multiple comparisons without adjustment Weak associations Aggregation obfuscates location Confounded by Social Class
Nasseri	Multiple comparisons without adjustment Aggregation obfuscates location Low statistical power Confounded by Social Class
Morgenstern	Multiple comparisons without adjustment Weak associations Aggregation obfuscates location; Distance is not dose Confounding by Social Class

Reasons for Scientific skepticism

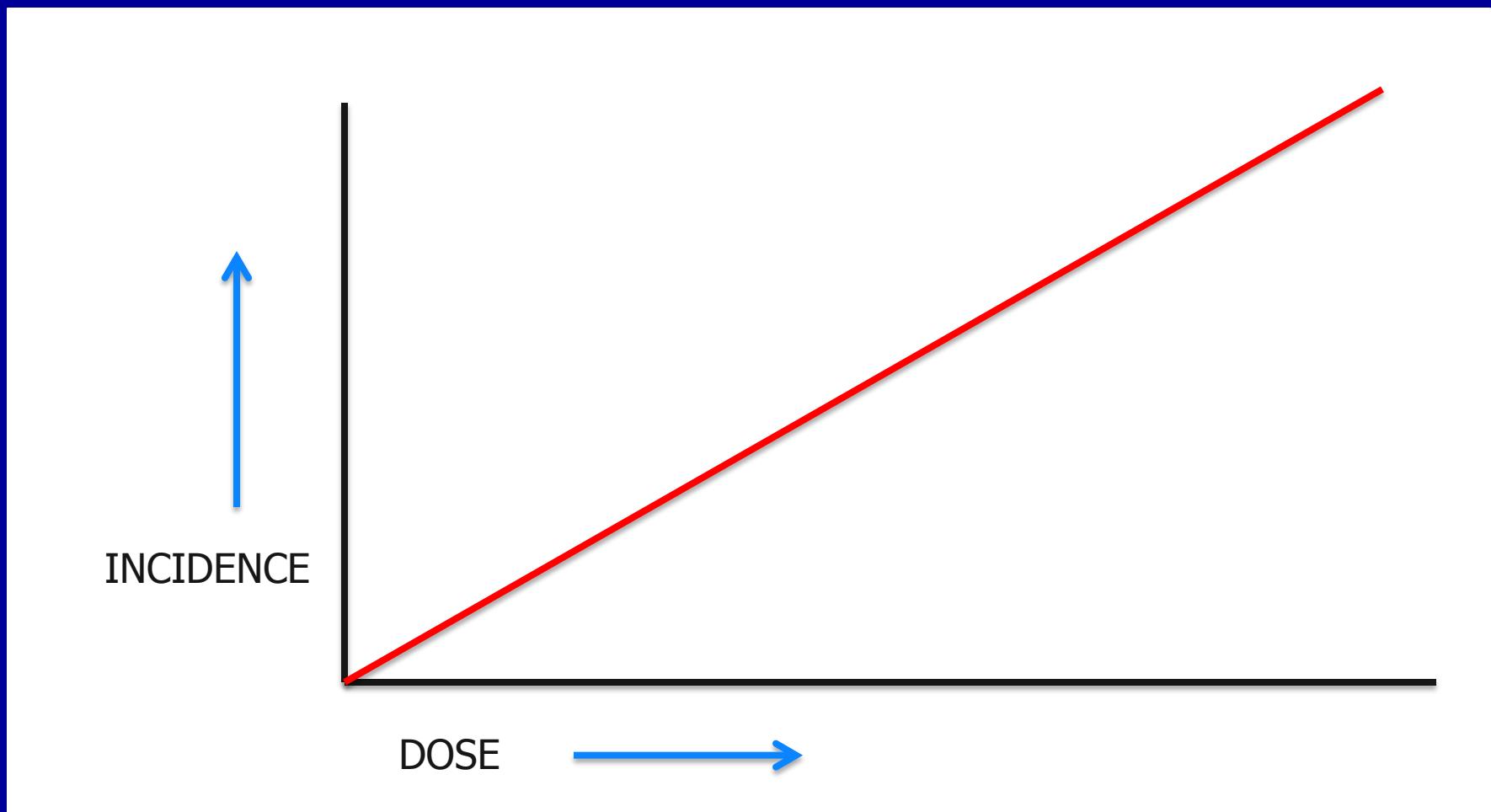
- Ambiguous and controversial exposure estimates
- The presence of a carcinogen, especially when technology permits detection of very low levels, does not necessarily constitute a major hazard
- High dose levels are needed to produce a measurable cancer excess

Effect of Industrial exposure to hexavalent chromium:

Mean level 790 micrograms/cubic meter of air



Carcinogenesis increases linearly with dose

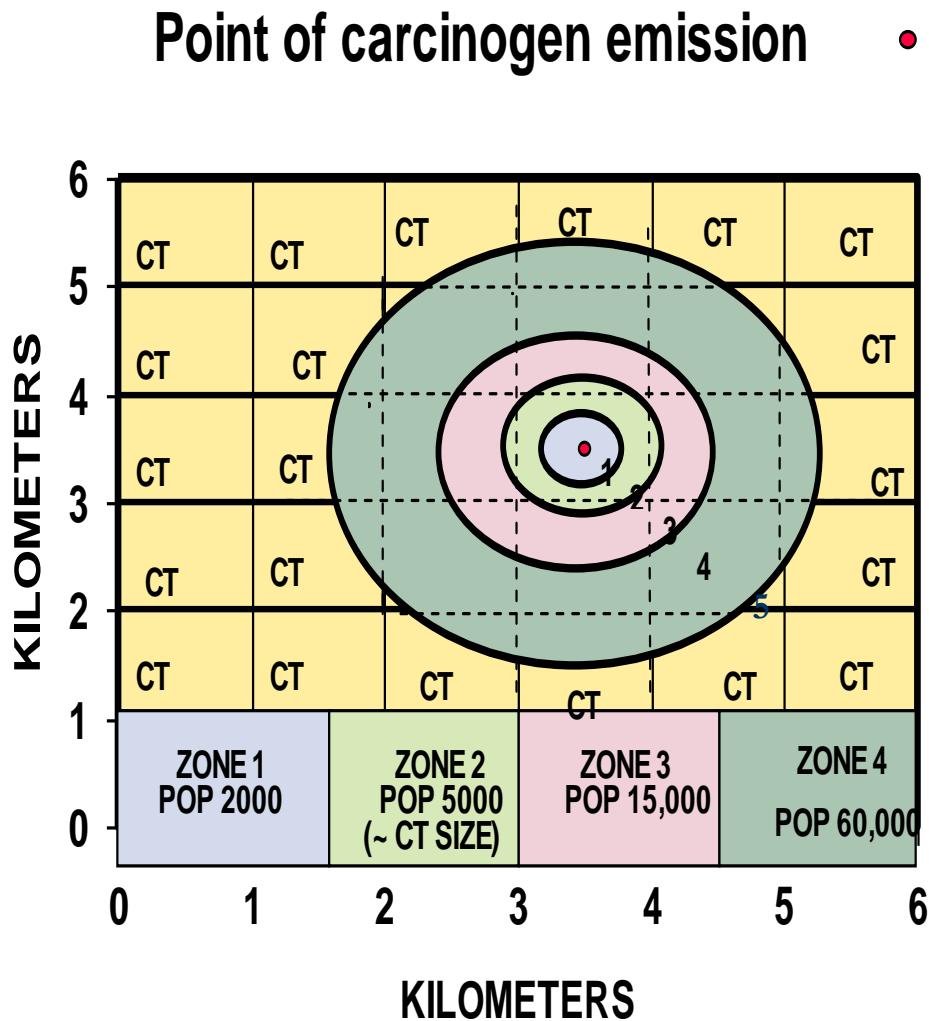


Projected effect of Strongest Community Exposure to Hexavalent Chromium

	Micrograms chromium ⁶ /m ³	Lung cancers /100,000
Workplace	790	1700
Community	0.04	0.09

Thus exposure at the point of the highest known emission of carcinogen in California, about one extra case per million would appear (i.e. in the average census tract, one extra case every 200 years)

Dispersion of carcinogen emissions



Emission dose level to individuals is variable

- Chemicals rapidly disperse into air/water
- As the distance from the site increases:
 - More people are exposed
 - Exposure dose is lower
 - Dispersion results in dilution: dose is inversely proportional to distance

Impact of point emission if dose is thought to double the risk

	Population	Distance	Attributable Risk	# Cases
At Source	50	0.1 km	100/100,000	0.05
Zone 1	2000	0.3 km	11/100,000	0.22
Zone 2	5000	0.5 km	4/100,000	0.20
Zone 3	15,000	1.0 km	1/100,000	0.15
Zone 4	60,000	2.0 km	0.25/100,000	0.15
Zone 5	120,000	3.0 km	0.10/100,000	0.12

No more than a single additional case would be expected

Reasons for Scientific skepticism

- Absence of historical precedents

Precedents: Environmental cancer clusters do occur (other than occupational risks)

Fallon, NV: 2000-2001, 16 ALL cases occurred, 0.3 expected
Host to thousands of diverse visitors

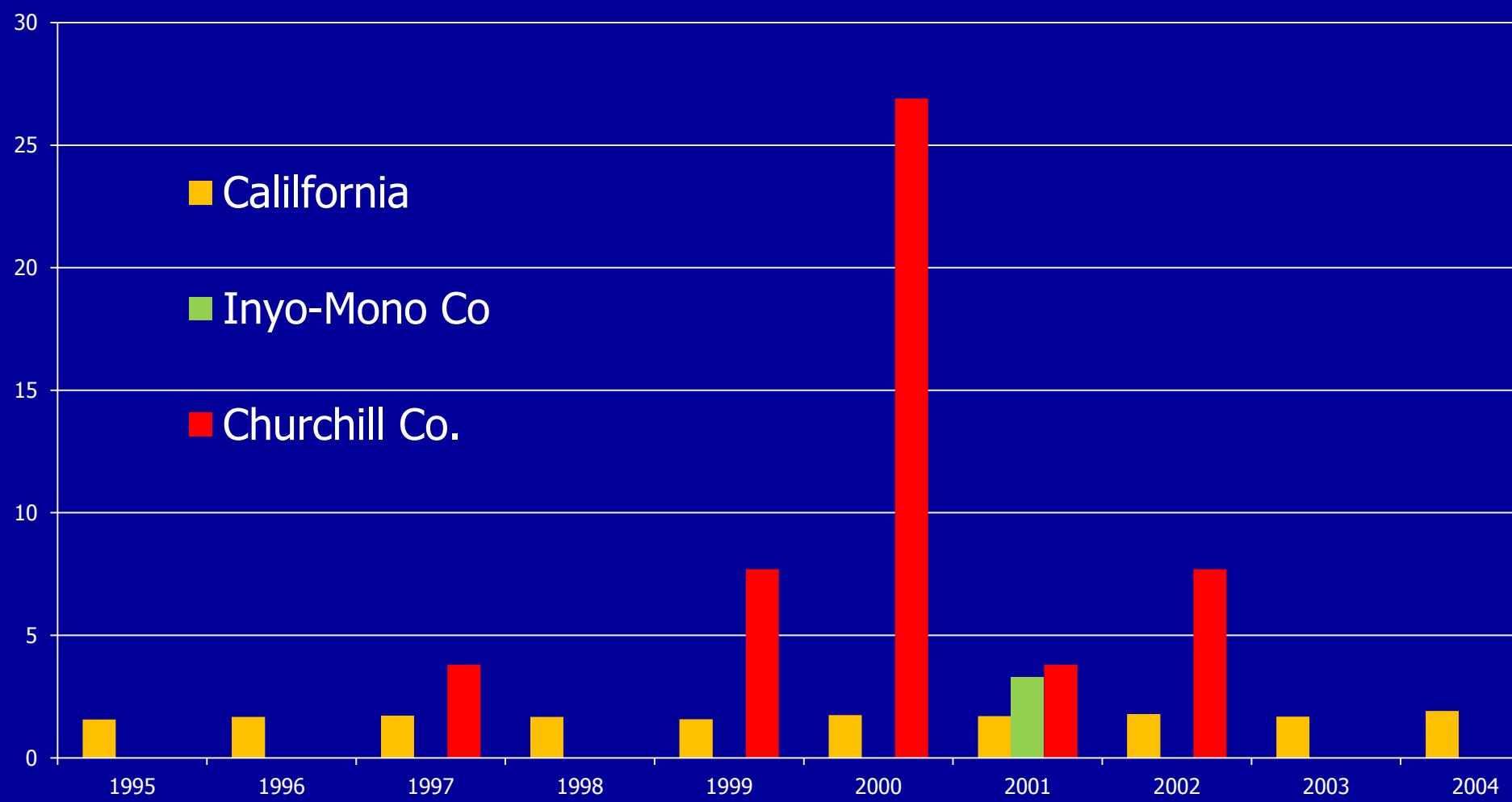
Libby, MT: Multiple cases of mesothelioma in a small town
Tailings of asbestos-containing vermiculite

Cappadocia, Turkey: Cluster of cases of mesothelioma
Greece, Italy, New Caledonia: Clusters of mesothelioma
From building materials or whitewash with asbestos

Ukraine/Belorus: Localized thyroid cancer in young persons
From nuclear fallout

Taiwan, Chile, Argentina, Bangladesh: Localized bladder cancer
Groundwater contaminated with natural arsenic deposits

Churchill County (Fallon) ALL Cluster Rate compared to California Rates



If dose is usually weak, why are “clusters” found? Two different circumstances

Strong direct exposure, highly targeted at close quarters

Household asbestos, person to person virus

Sufficient dose by *short-term but intense* exposure

Sufficient dose to **single families or compounds**

Strong indirect or distant exposure, disseminated by air/water/soil

Chernobyl, waterborne arsenic, asbestos tailings

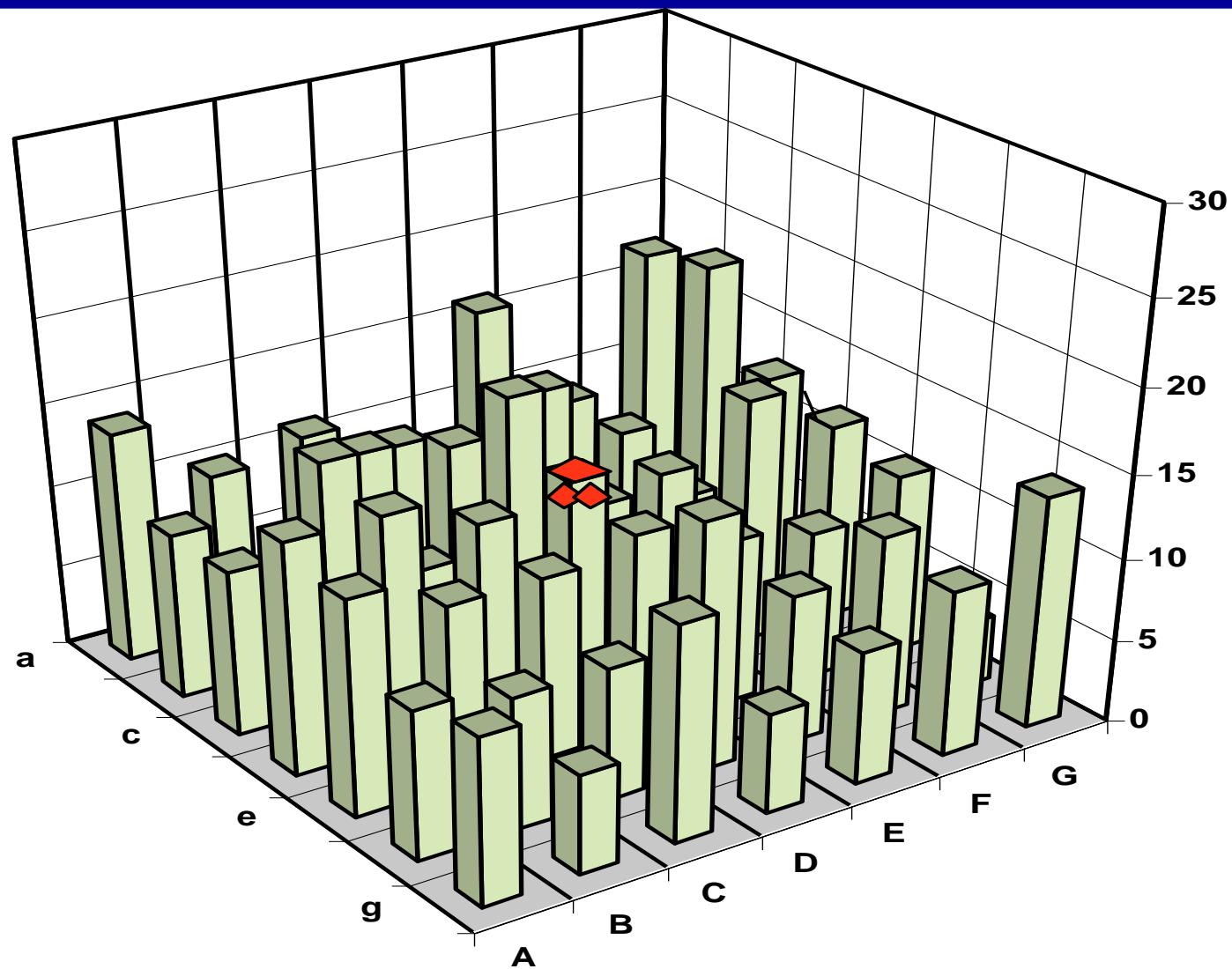
Sufficient dose by **continuous cumulative** exposure over the long-term

Sufficient dose disseminated to **multiple adjacent localities**

Weak exposure

Rare cancers undetectable, common ones lost within random variation

dom (Poisson) distribution of Lung Carcinoma
If the cancer is not rare, the usual cases outnumber the
rare ones by many times. +
ring in 49 Localities of 5000 Persons each over
added ones (and vary in number by chance)
+ Unexpected Cases?



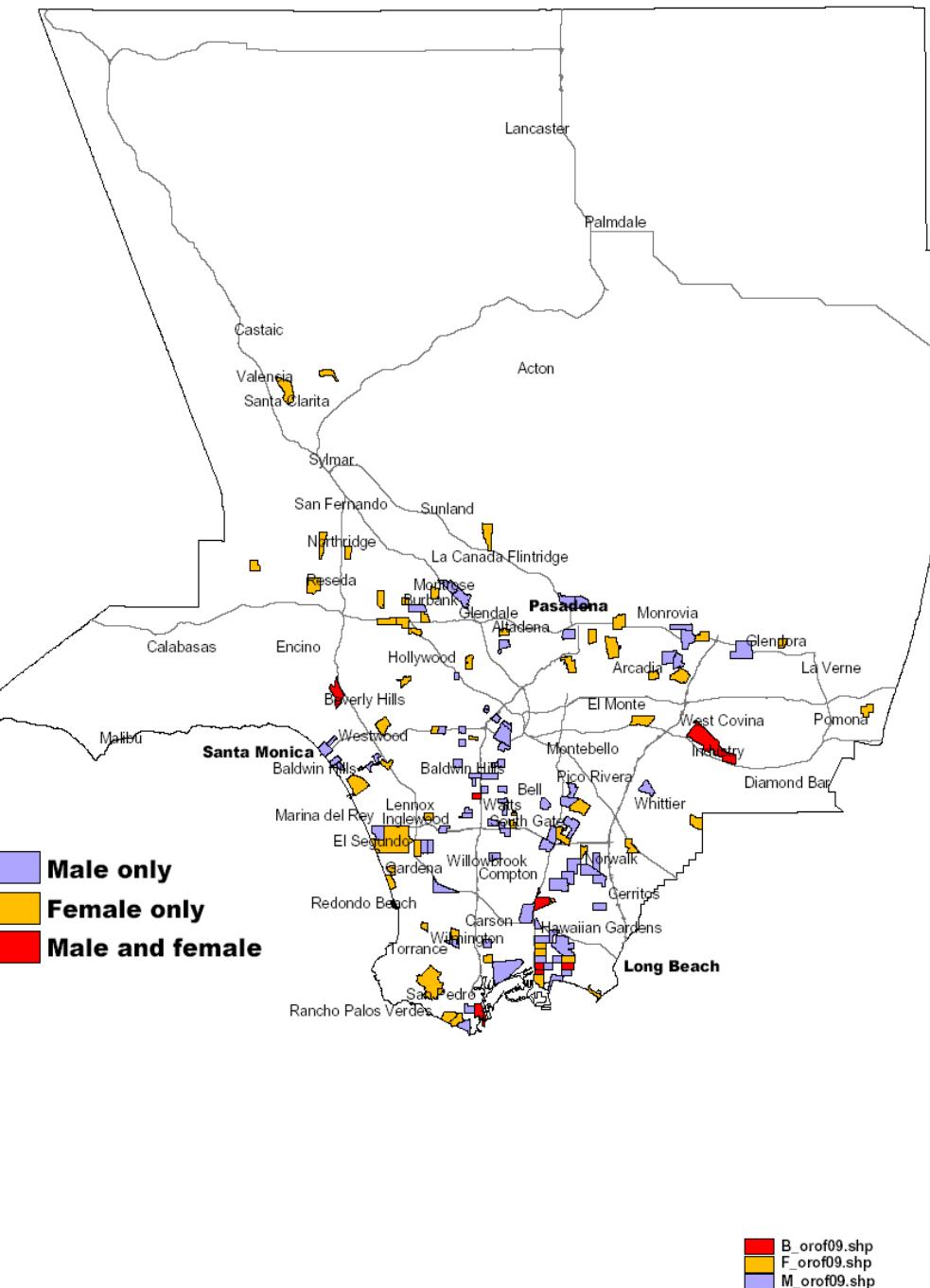
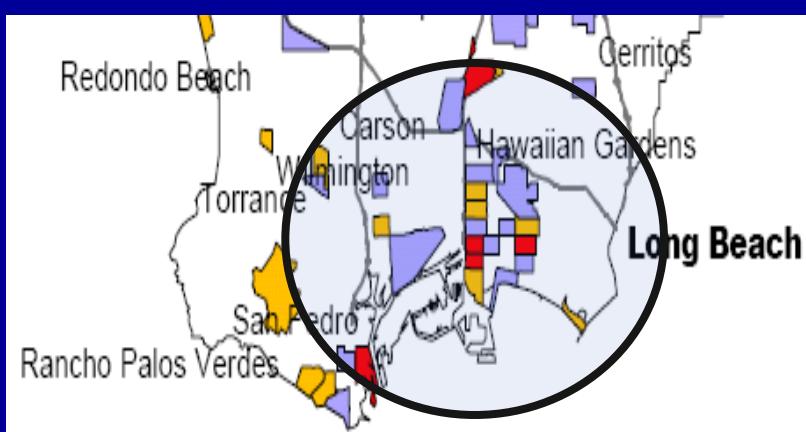
The Challenge

- Some offside residents may have been exposed to carcinogens at ***some*** dose
- They may well have ***some*** added cancer risk.
- The challenge is to see if a ***measureable and unambiguous*** increase in risk has been produced.
- Must examine ***individual*** neoplasms and ***individual*** tracts

To demonstrate an unambiguous association:

- Increase must be at least 50%, a relative risk of 1.5 (there are too many alternative explanations for a weaker link)
- Chance must be excluded
- Adjacent tracts (localities) offsite should have high exposure in common
- Here is a local example

Carcinoma of the Oropharynx



Steps in Linking Environmental Carcinogenicity to a Particular Locality

1. Assess the likelihood that any association between cancer incidence and a residential locality could be explained ***by chance***
2. Ensure that any such association cannot be explained by ***a bias***
3. Ensure that any such association cannot be explained by the ***characteristics of local residents?***

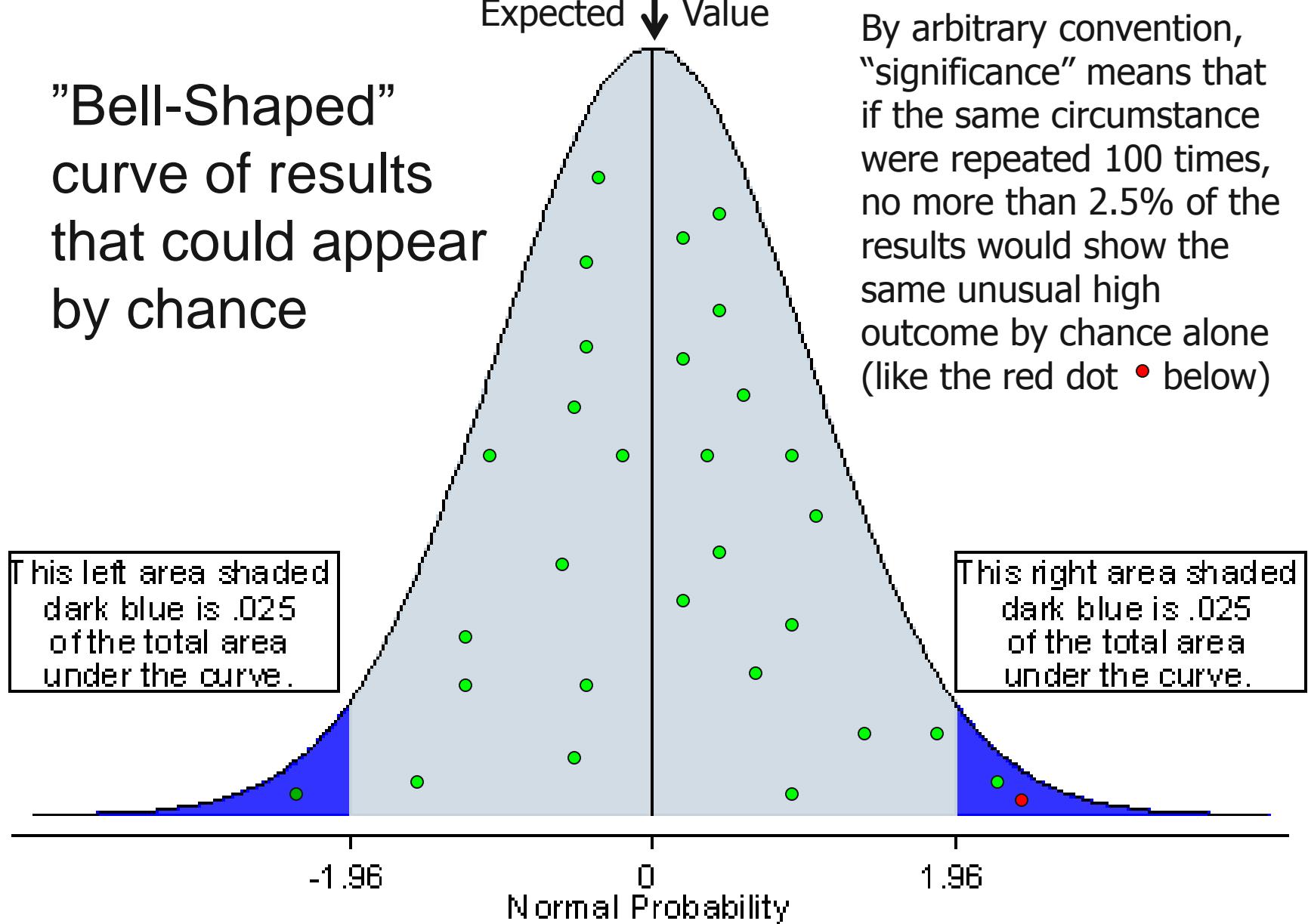
1. Assessing chance

- The conventional method is to identify by computation any excess difference which is statistically significant at the level of 95% confidence
- Method is based on the appropriate distribution of random possible results—chance can never be ruled out, just quantified at an arbitrary level.
- We perform this exercise to screen tract/cancers

"Bell-Shaped"
curve of results
that could appear
by chance

This left area shaded dark blue is .025 of the total area under the curve.

Expected ↓ Value

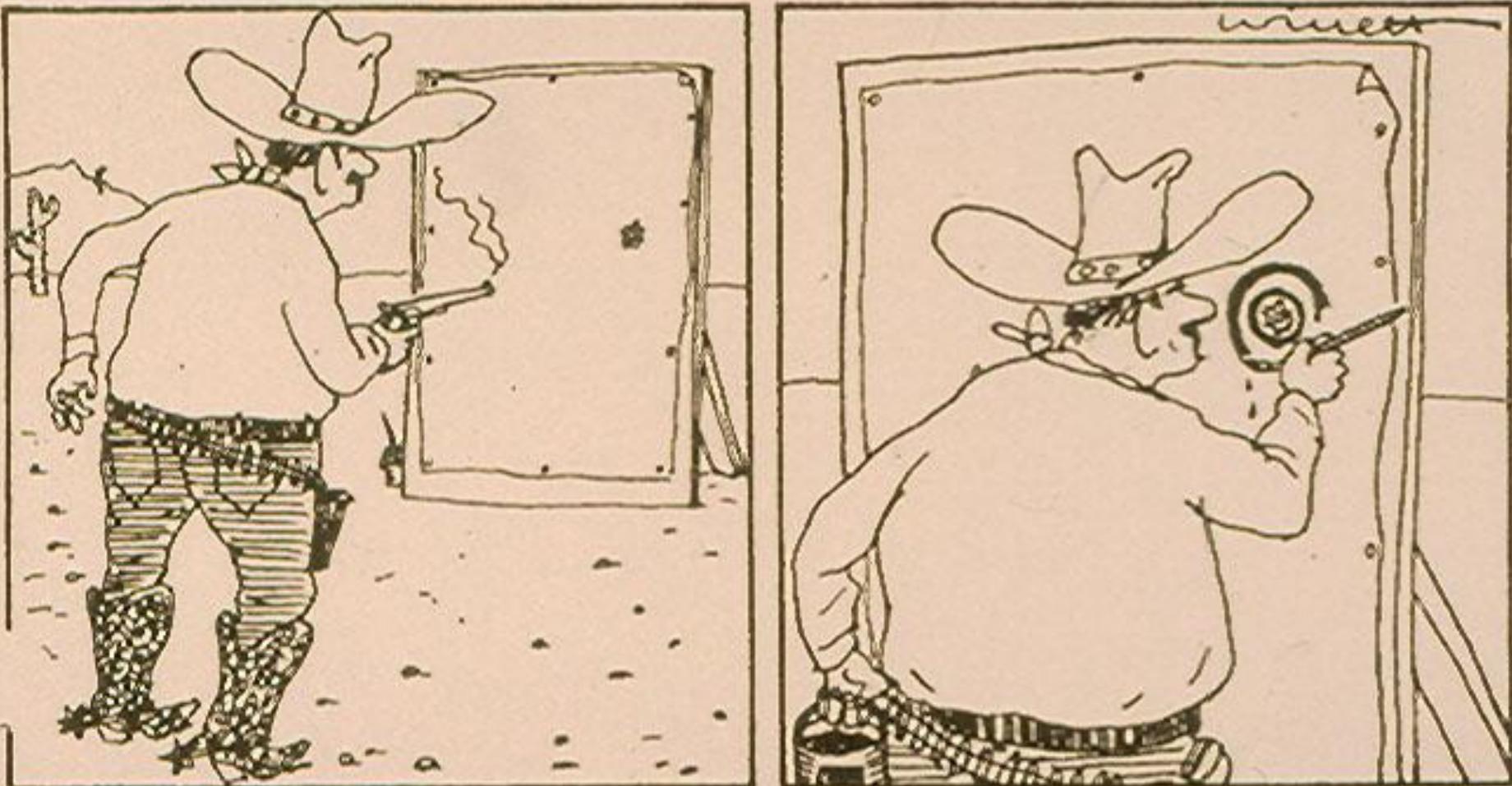


By arbitrary convention,
"significance" means that
if the same circumstance
were repeated 100 times,
no more than 2.5% of the
results would show the
same unusual high
outcome by chance alone
(like the red dot • below)

2. Bias comes in several forms

- Registry errors: unlikely, because ascertainment is very complete and in effect done blindly to place, age, race, etc.
- Census errors: underestimation of the number of persons, especially high risk persons, makes the excess look too large. This is a common problem in rapidly changing neighborhoods
- Texas sharpshooting: If investigation is initiated by a reported “cluster”, we already know the rate is not going to be low, and the statistical test is meaningless

“TEXAS SHARPSHOOTING”



AIM, SHOOT, AND ONLY THEN--
DRAW THE TARGET

Multiple Comparisons

- .
- The more cancers, periods, and tracts tried, the more likely are extreme findings
- Solution: instead of relying upon “significance” for each tract/cancer, we screen all tract-cancer combinations by significance, then calculate how often each extreme result could occur by chance among all CA tracts
- The following Poisson table gives this percentage for selected observed numbers given the number expected.

Percent of searches expected to find N or more cases observed according to the mean expected

Mean expected	1 Obs	2 Obs	3 Obs	4 Obs	5 Obs	6 Obs	7 Obs	8 Obs	9 Obs	10 Obs	11 Obs	12 Obs
1	63.2%	26.4%	8.0%	1.9%	0.4%	0.1%	0.01%					
2		59.3%	32.2%	14.2%	5.2%	1.6%	0.4%	0.1%	0.02%	0.01%		
3			58.4%	36.0%	19.2%	9.1%	3.4%	1.2%	0.4%	0.1%	0.03%	
4				56.7%	37.1%	21.5%	11.1%	5.1%	2.1%	0.8%	0.3%	0.1%
5					55.8%	38.3%	23.7%	13.3%	6.8%	3.2%	1.3%	0.5%
6						55.4%	39.3%	25.5%	15.2%	8.3%	4.2%	1.9%
7							54.9%	40.0%	27.0%	16.9%	9.8%	5.3%
8								54.8%	40.8%	28.4%	18.4%	11.3%
9									54.3%	41.1%	29.2%	19.5%
10										45.3%	32.8%	21.4%

For example:

- When 2 cases are expected and 6 are observed, 1.6% of localities of that size would find as many or more than 6 by chance.
- That means in 160 California localities

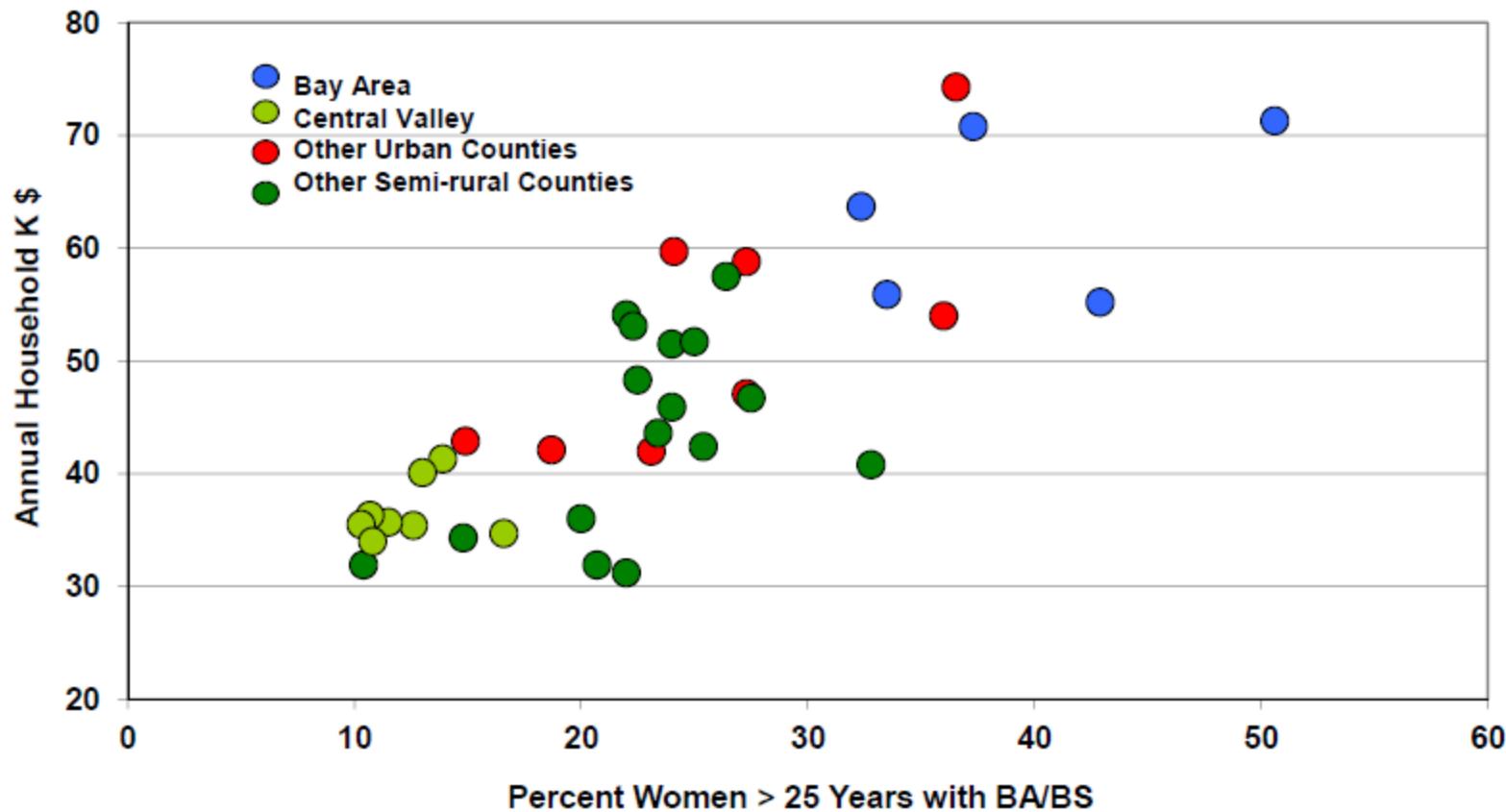
3. Explore alternative explanations for any cluster: ***They are important considerations***

- Other known causes of that particular cancer
 - Rarely measureable by locality: example--smoking
- Race/Ethnicity, (approximate by tract)
 - Measureable surrogate causes like—skin color
- Education and Income (approximate by tract)
 - Measureable surrogate for causes like—sexual and reproductive history

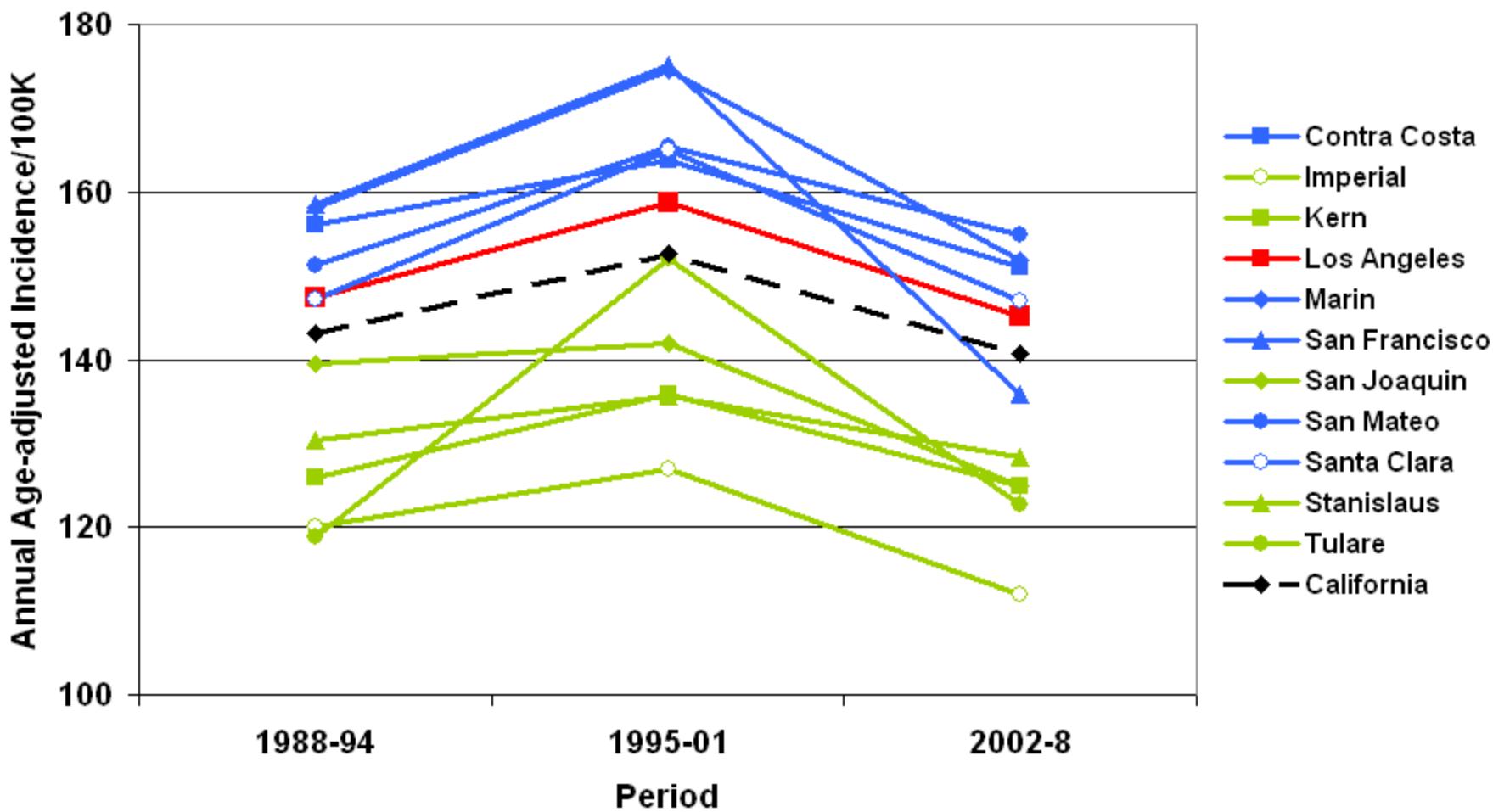
A rough commonality of lifestyle characterizes the residents of any neighborhood

- Neighborhood choice is personal and particular
 - Preferred location, location, location
- Thus birds of a feather tend to flock together
- Obvious on both County and Census tract levels
 - Ethnicity, education, friends, habits, occupation
- Shows up in cancer patterns

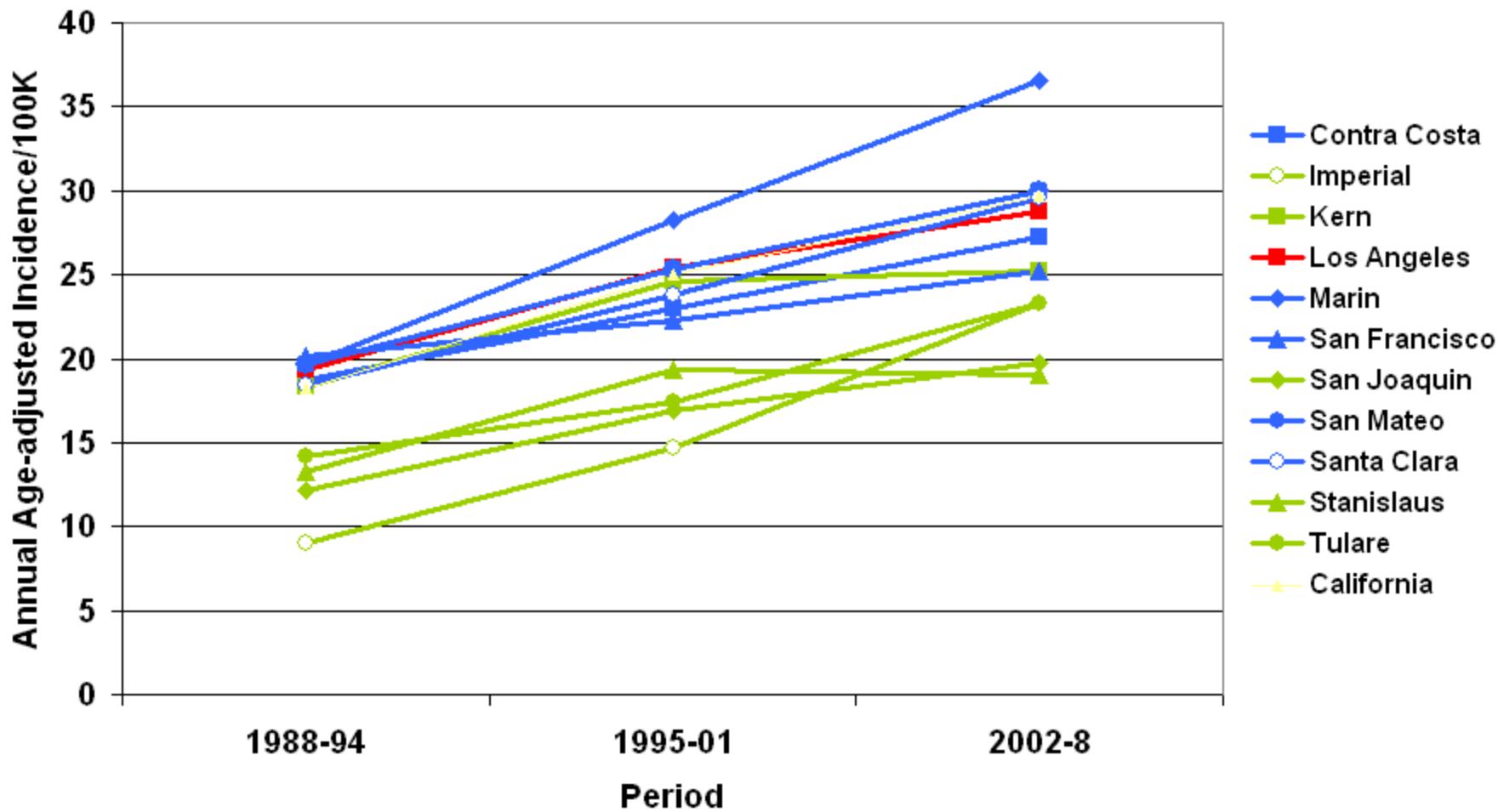
California County Median Household Income
According to Percent of College-Educated Adult Women
(Counties of more than 50K)



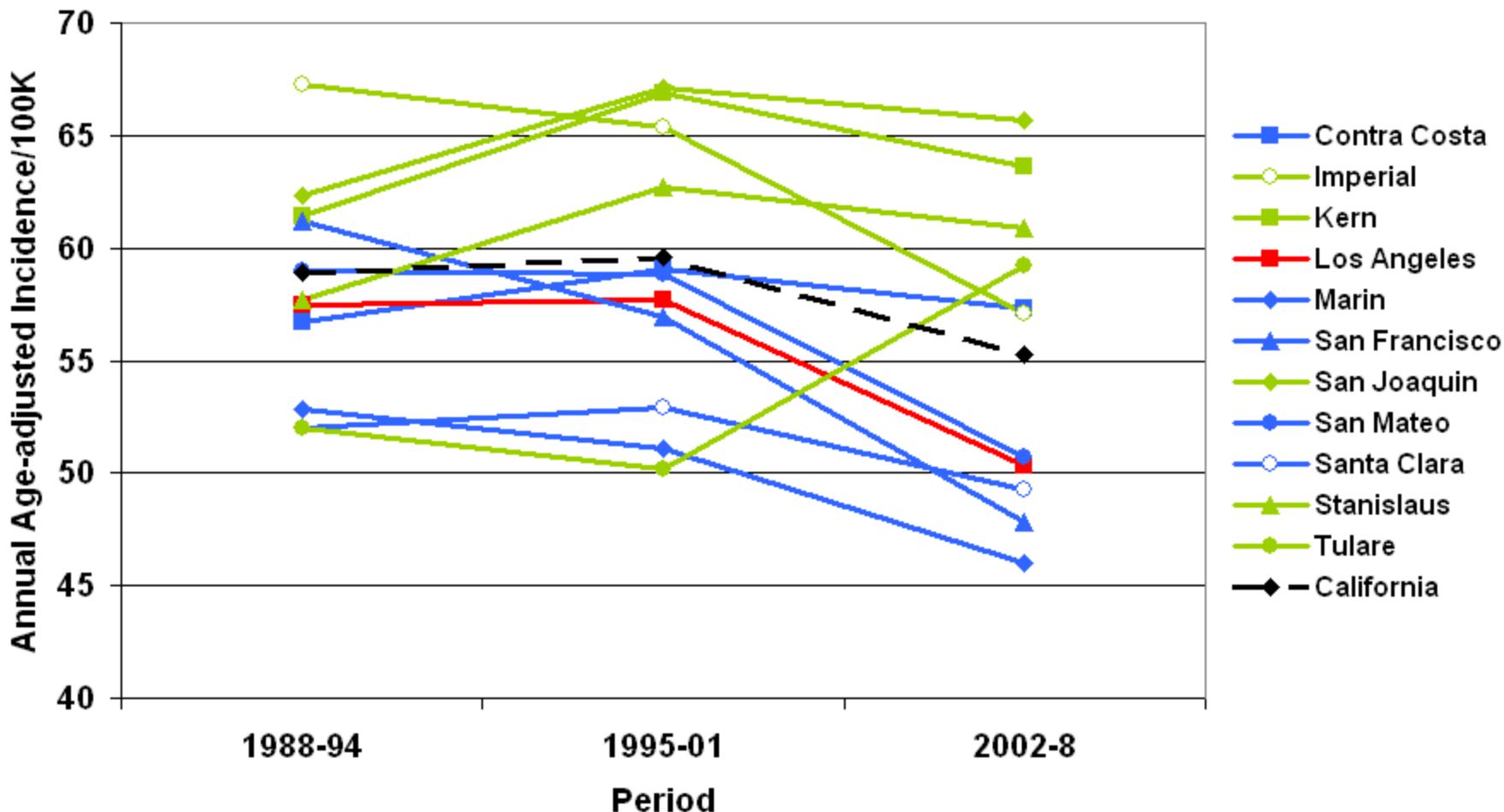
**Trends in Incidence of Breast Cancer among White Females
from California Counties differing in Median Income and Educational
Attainment**



**Trends in Incidence of Malignant Melanoma among Whites
from California Counties differing in Median Income and Educational
Attainment**



**Trends in Incidence of Female Lung Cancer among Whites
from California Counties differing in Median Income and Educational
Attainment**

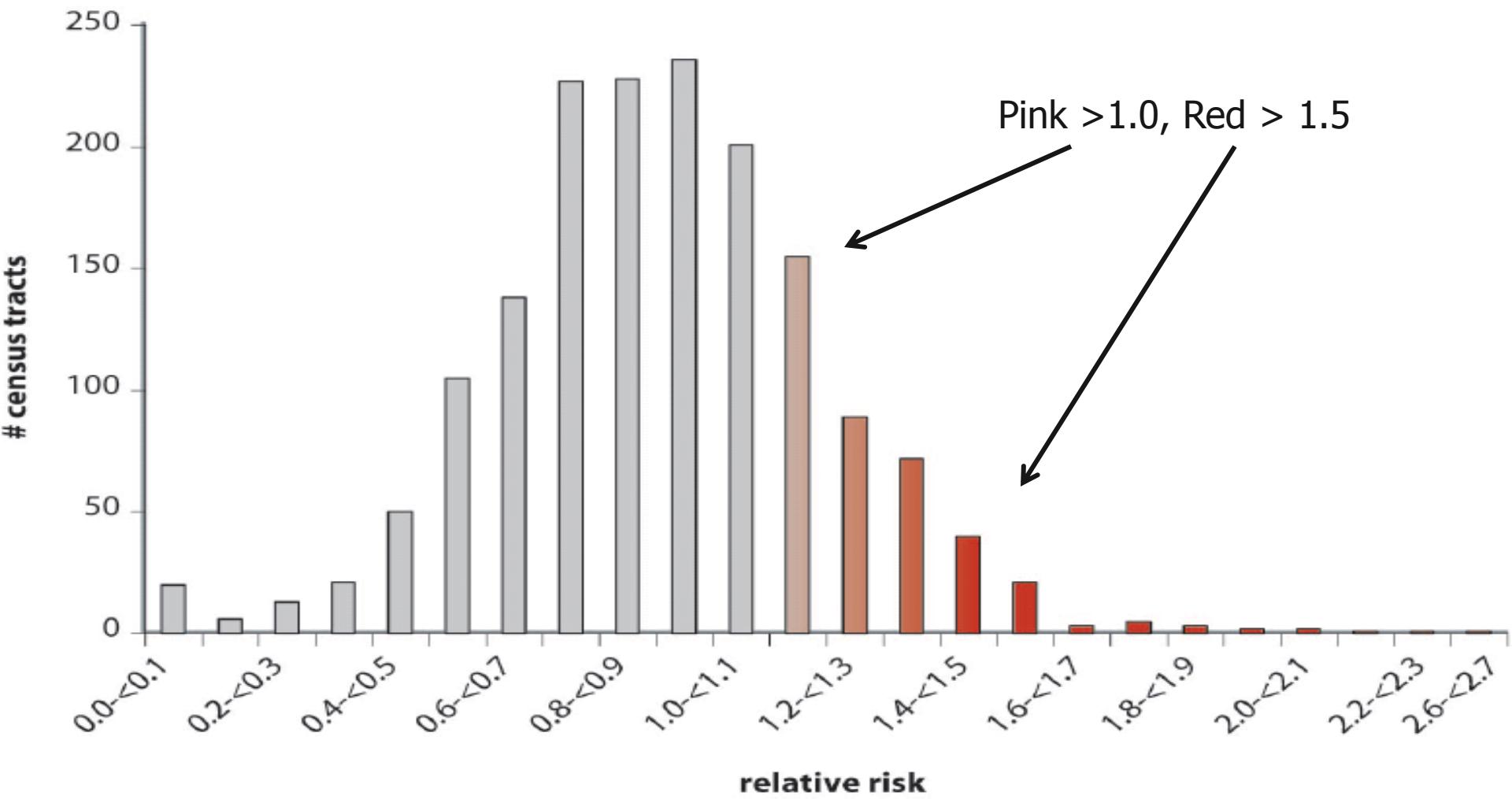


From Counties to Census tracts

- We define localities as census tracts because the census gives us accurate populations by age and sex
- Census tracts are smaller than counties, averaging about 5000 persons but varying in size from hundreds to tens of thousands
- Thus variation in cancer occurrence comes from three factors, usually in this order:
 - Size of the tract population
 - Chance
 - Prevalence of causal factors

Colon Carcinoma in LA

**Distribution of census tracts by relative risk
(males)**

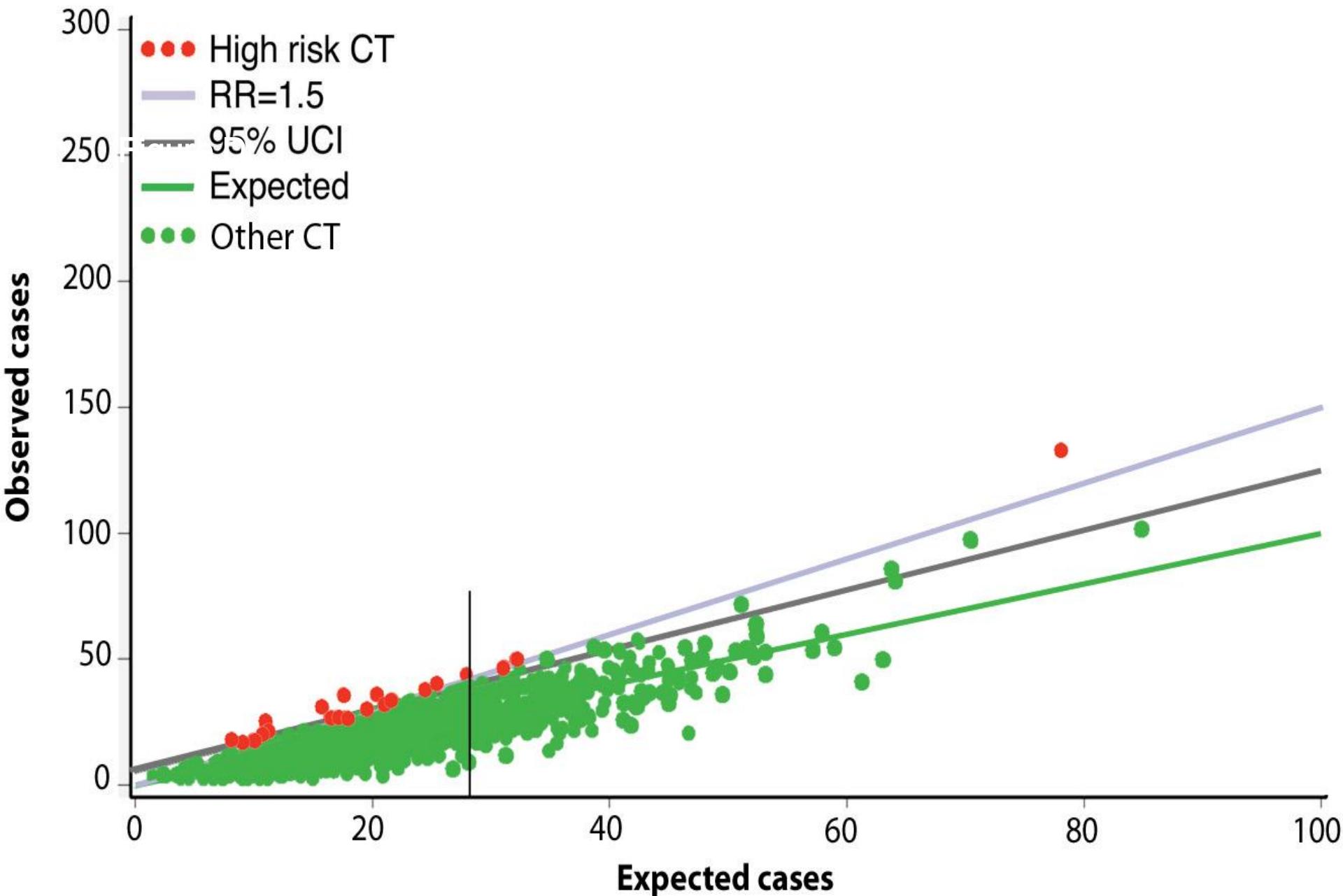


Because the tract size varies, we can describe the tracts by the number of cases expected and observed rather than by rate

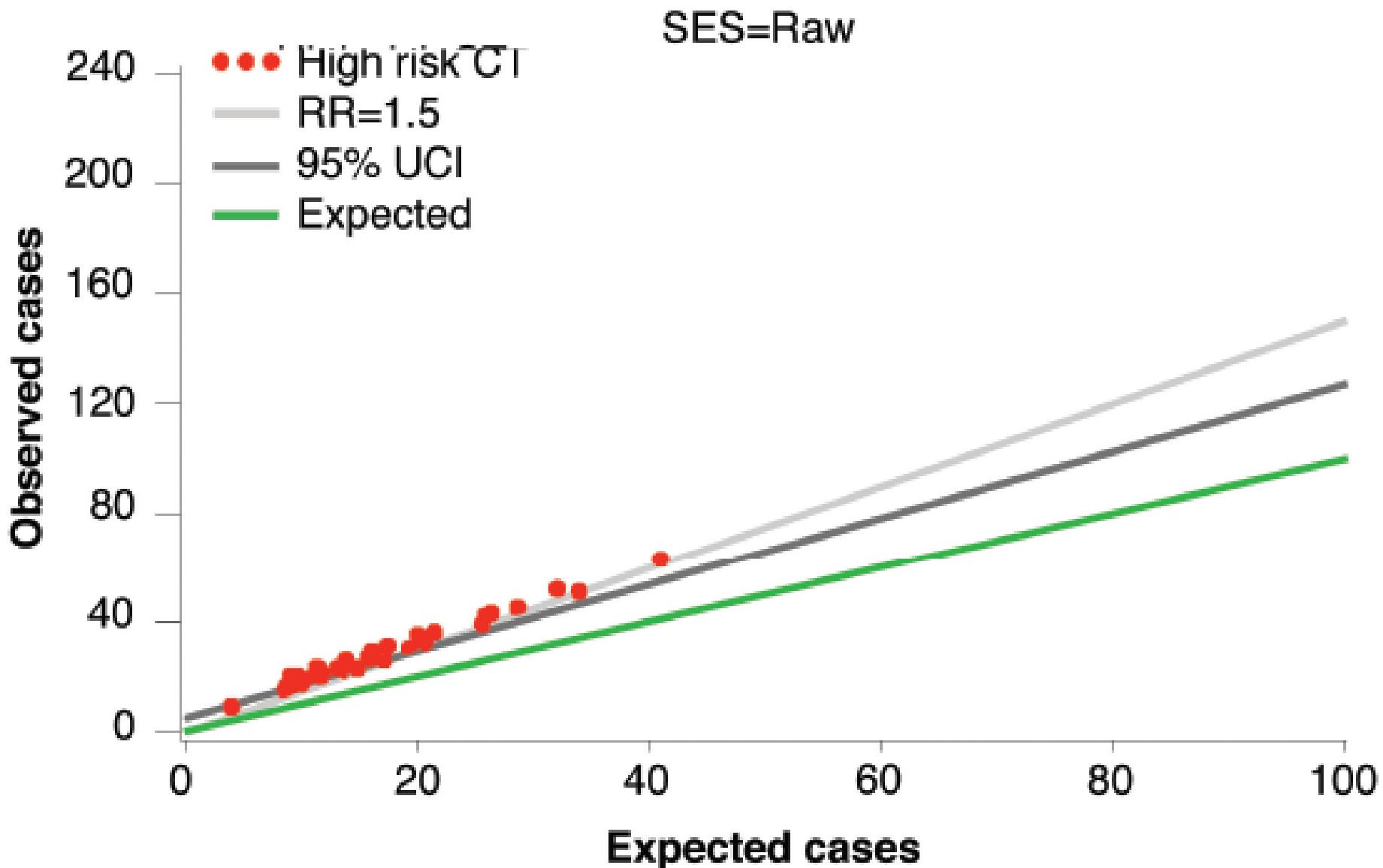
- For a given expected case number horizontally, we represent each tract vertically by a dot for the observed case number
- Lines showing both a standard risk (50% increase) and a measure of “significance” are shown.
- A dot above the lines in red represents a “significant” increase.
- Those occurring by chance will usually touch a line. The higher the red dot, the higher the incidence.
- Different cancers show different patterns depending on how localized high risk is found

Census Tracts at high risk of COL

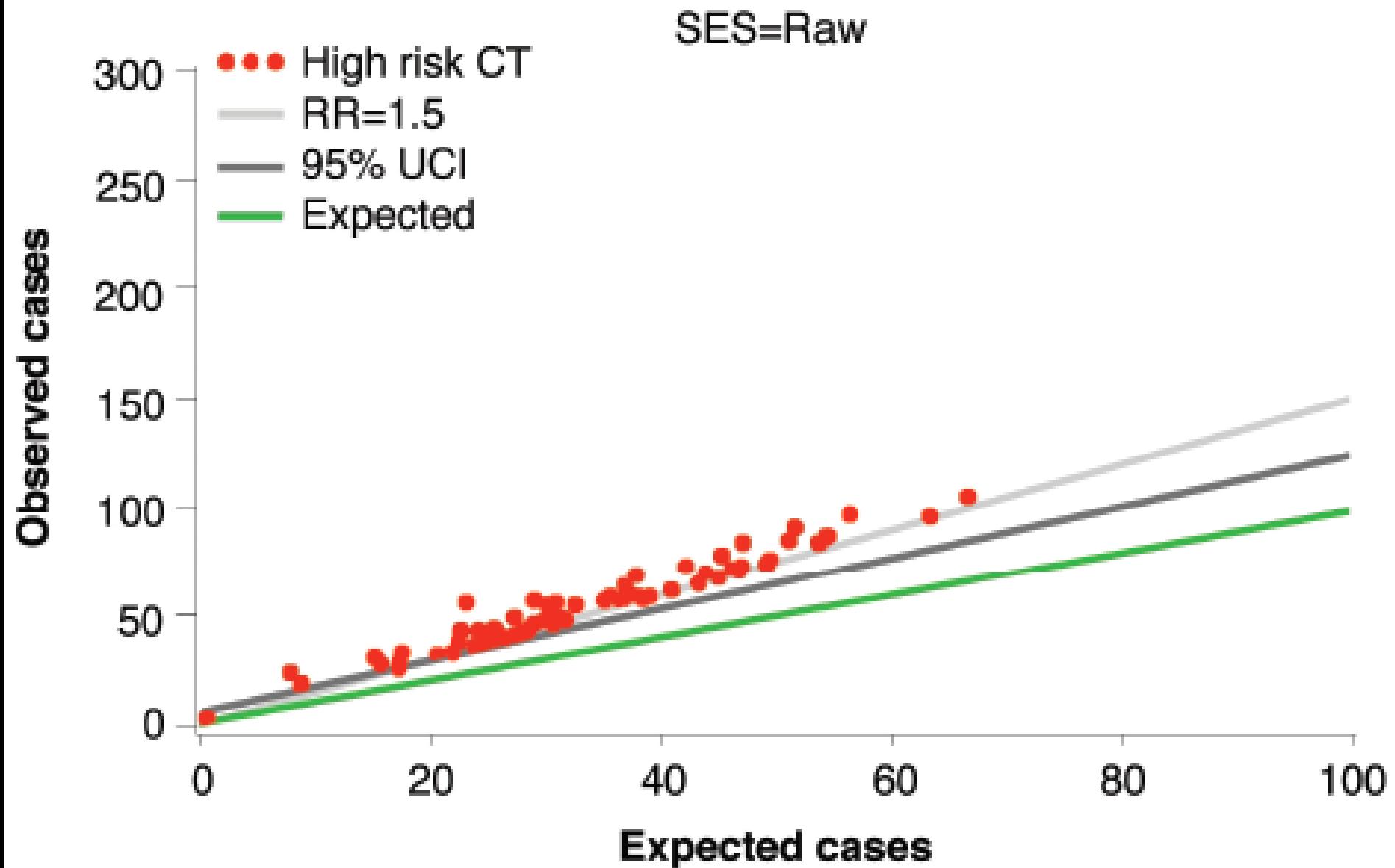
according to the number of observed and expected cases



Female Colon Cancer

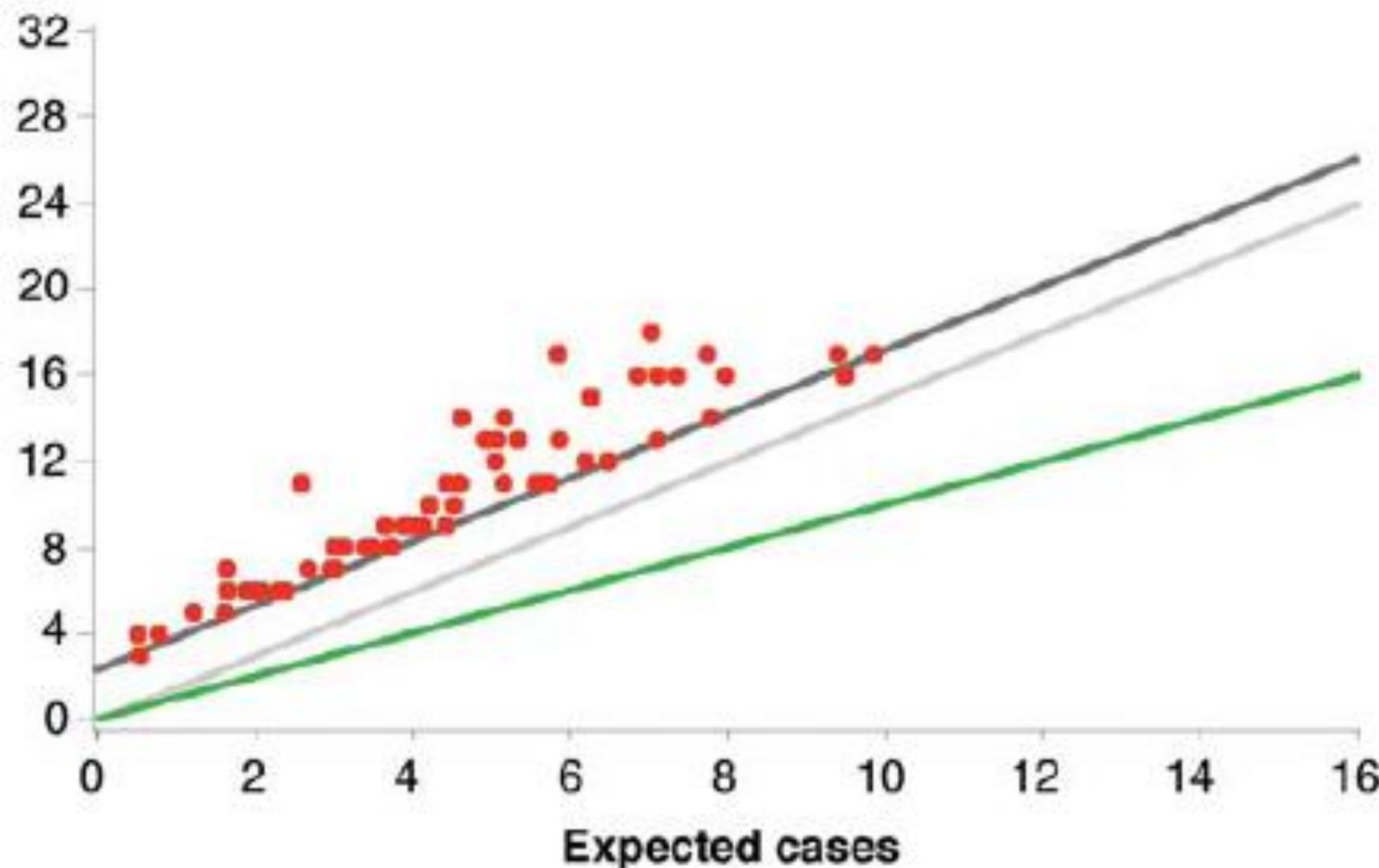


Male Lung Cancer



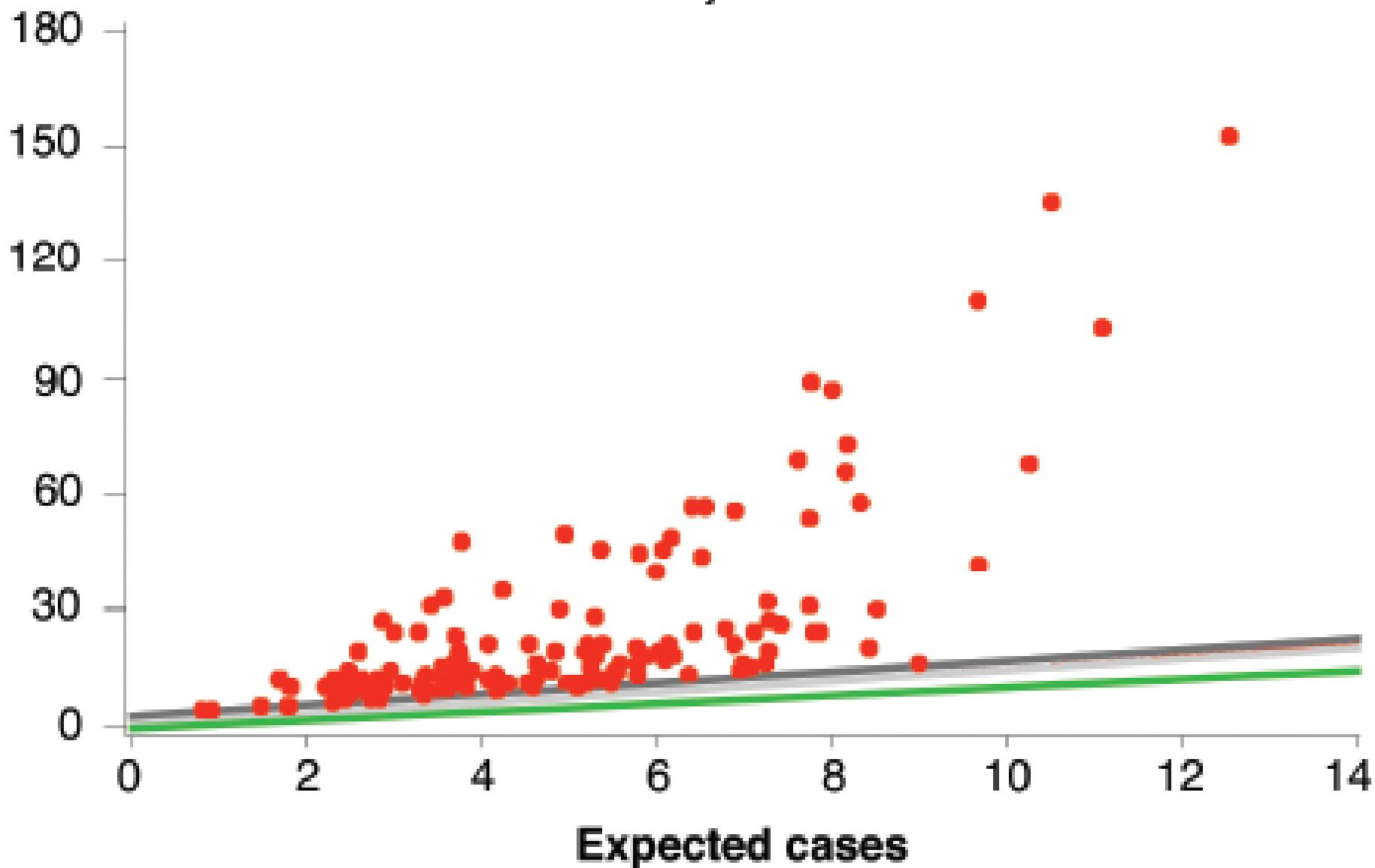
Female Oropharyngeal Cancer

SES=Adj for SES

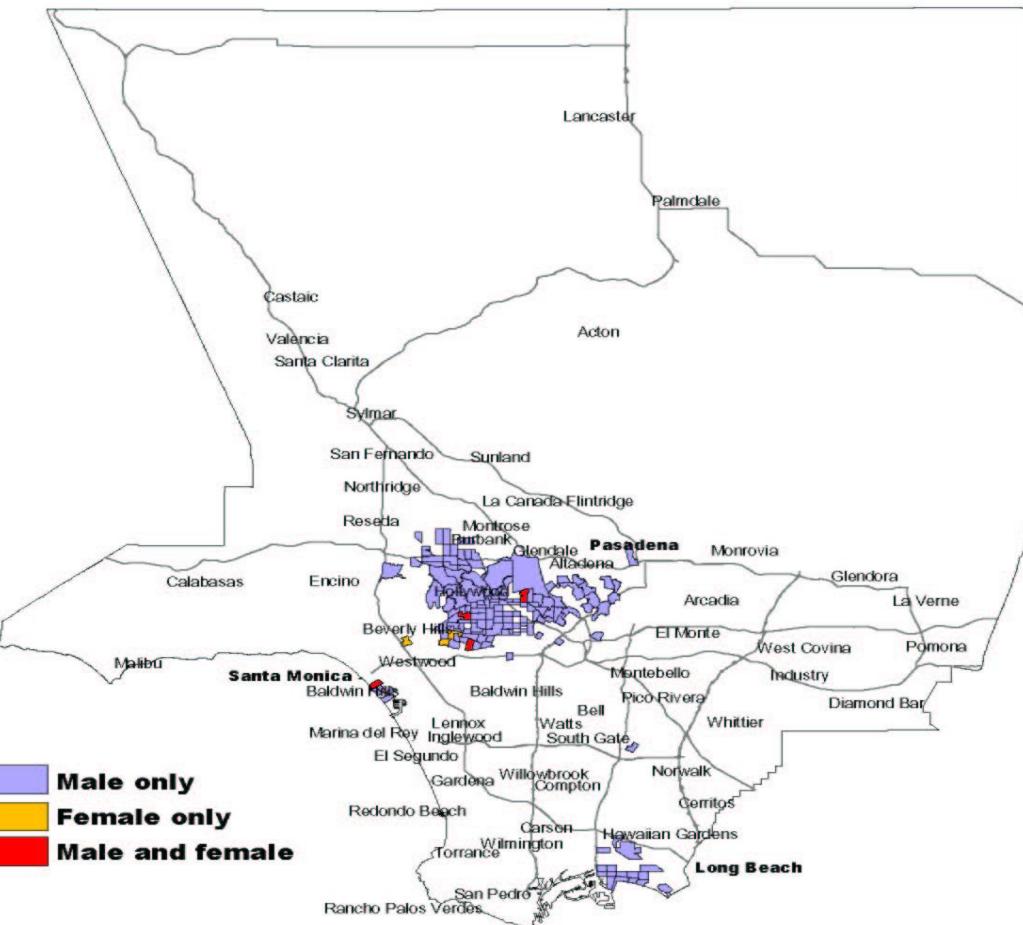


Male Kaposi Sarcoma

SES=Adj for SES

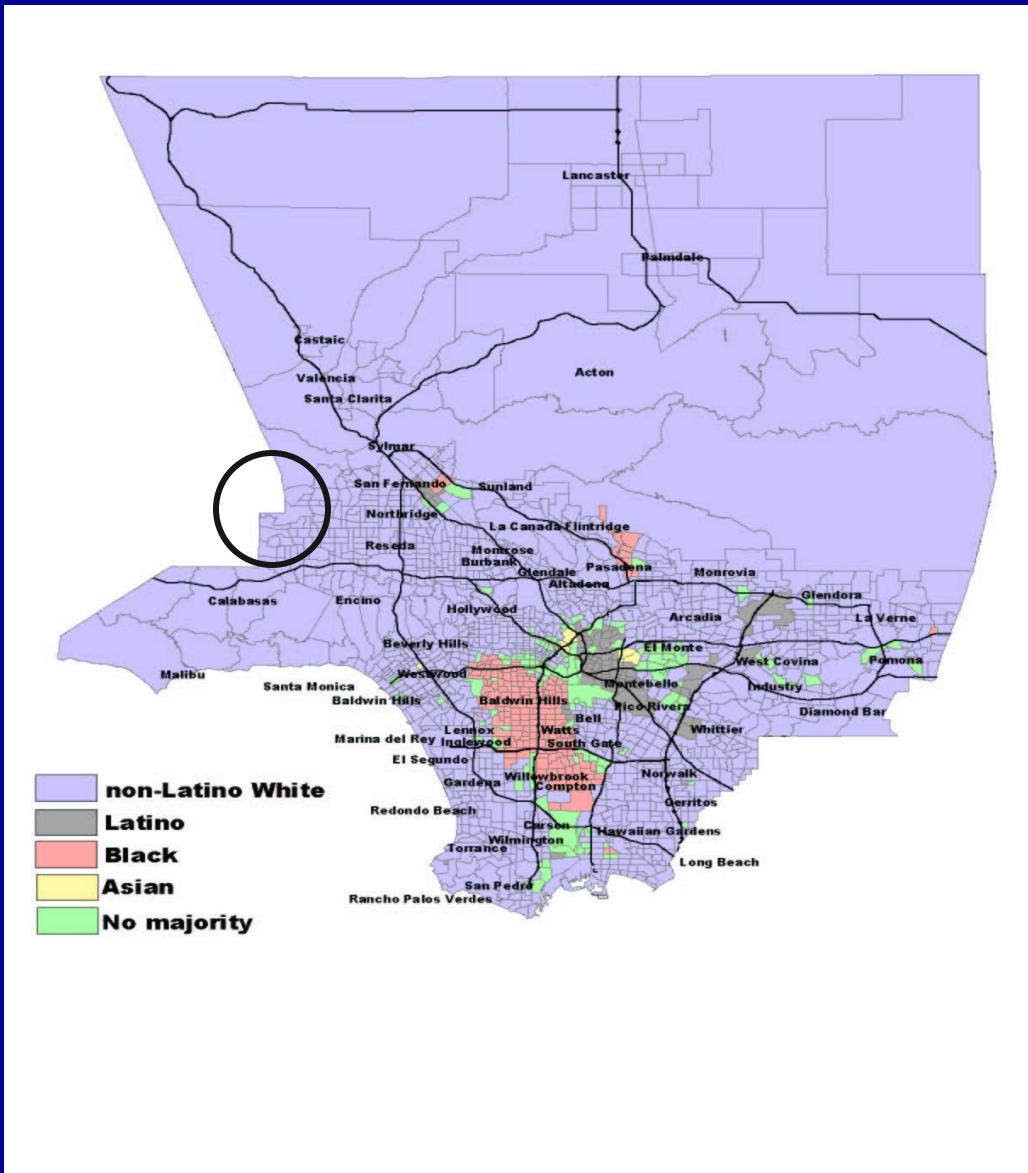


KAPOSI SARCOMA



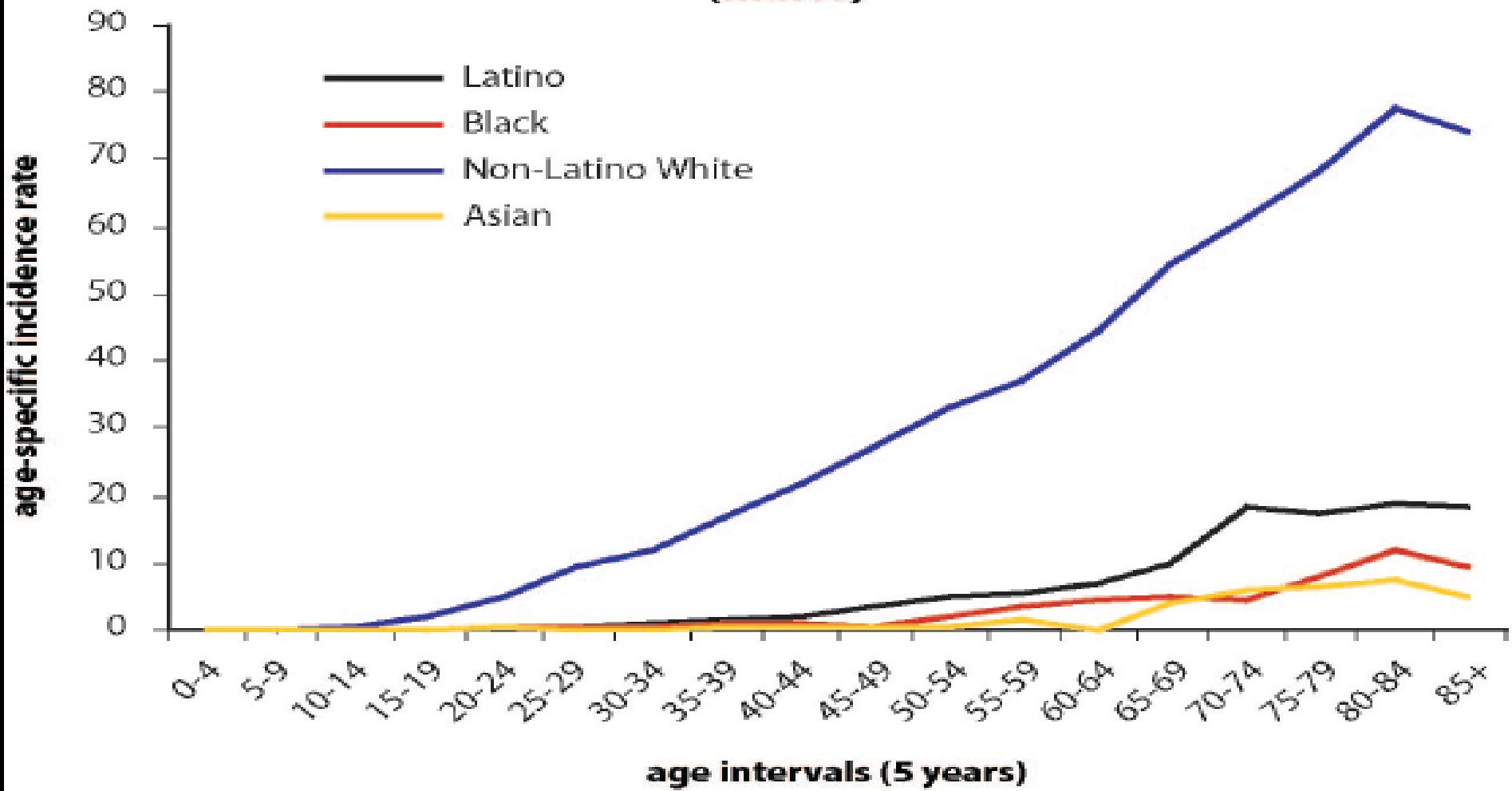
B_kapf09.shp
F_kapf09.shp
M_kapf09.shp

CENSUS TRACTS BY MAJORITY CASE RACE/ETHICITY



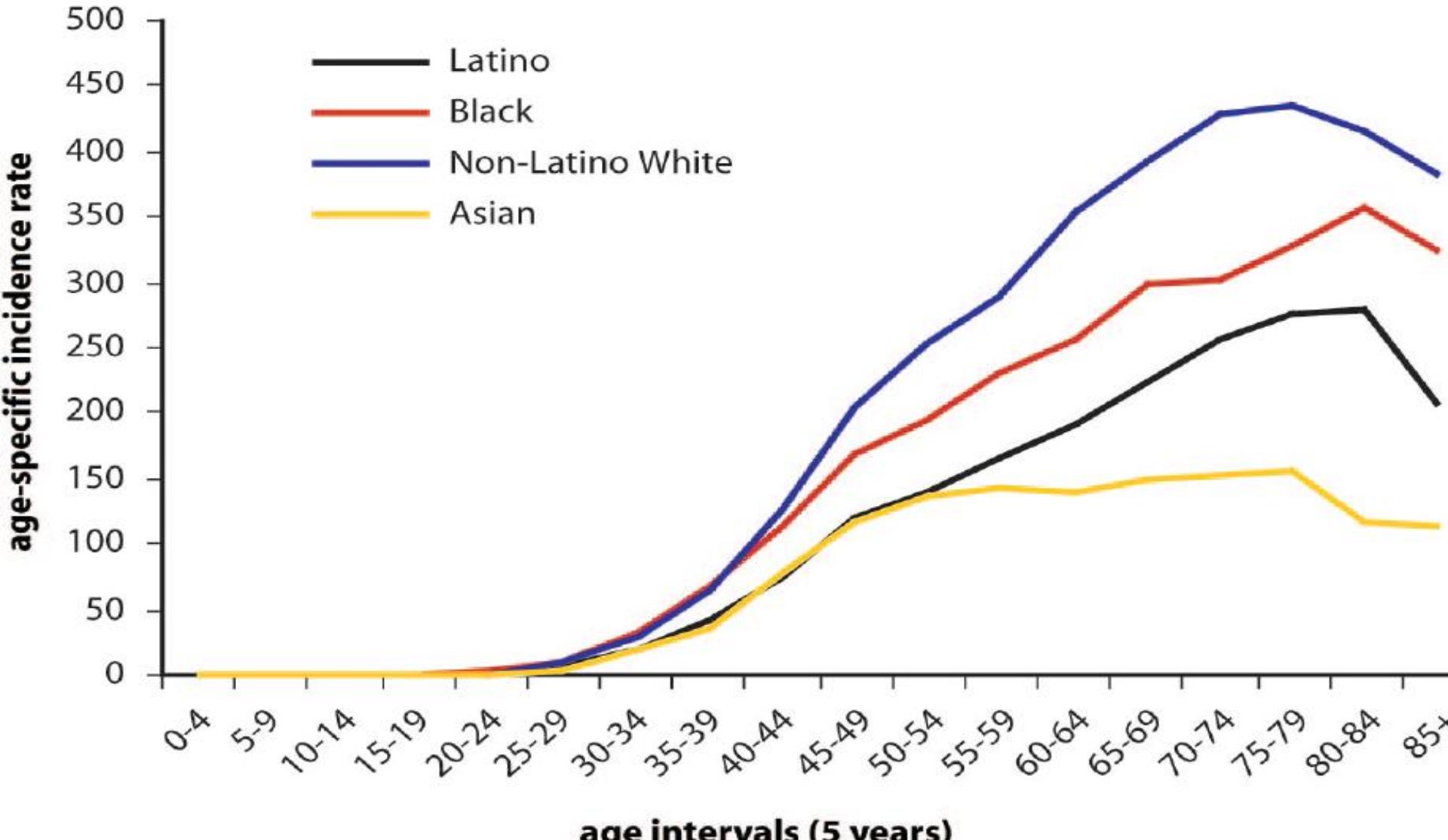
Malignant Melanoma

**Age-specific incidence by race/ethnicity
(males)**



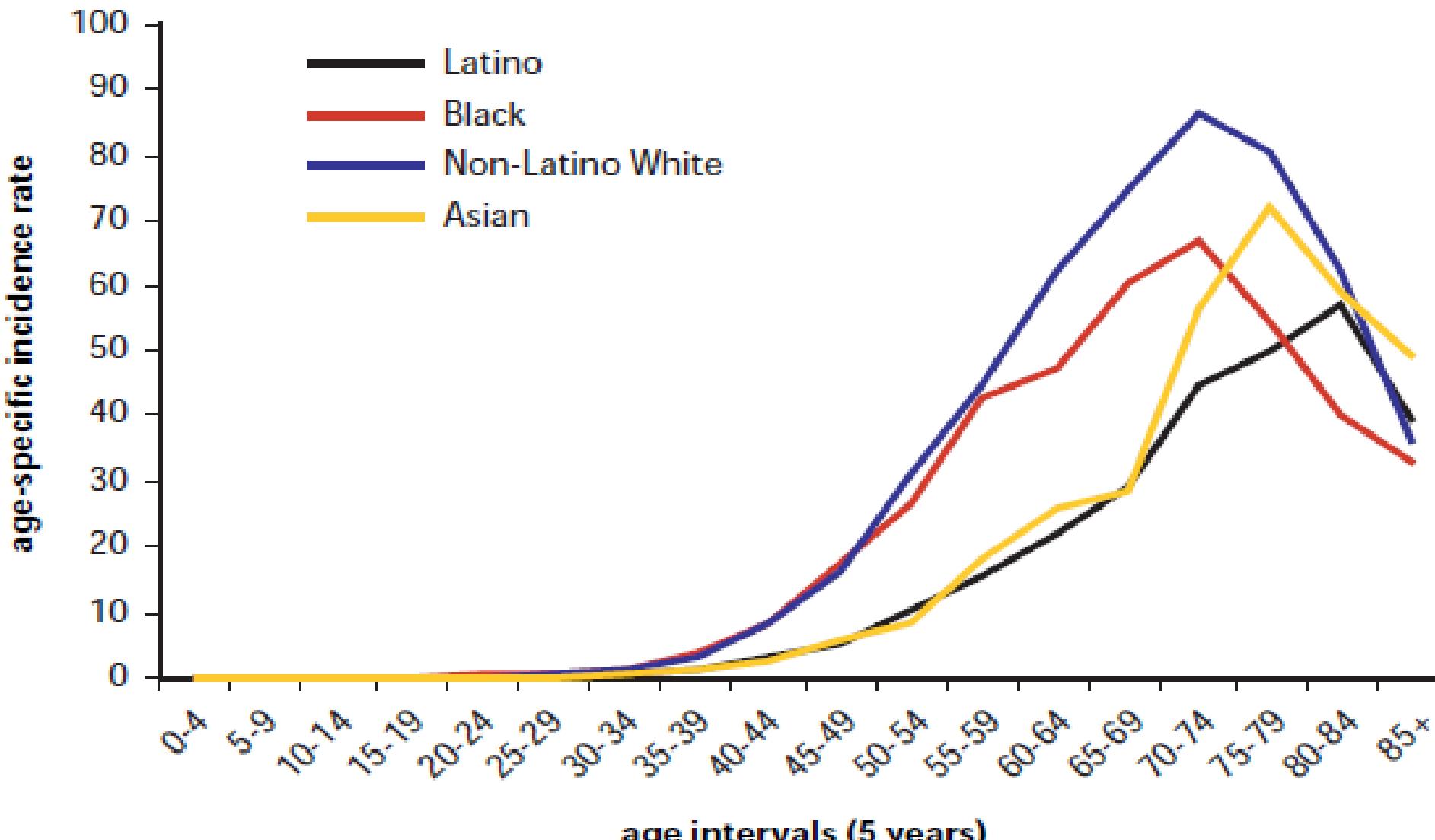
Female Breast Cancer

Age-specific incidence by race/ethnicity (females)



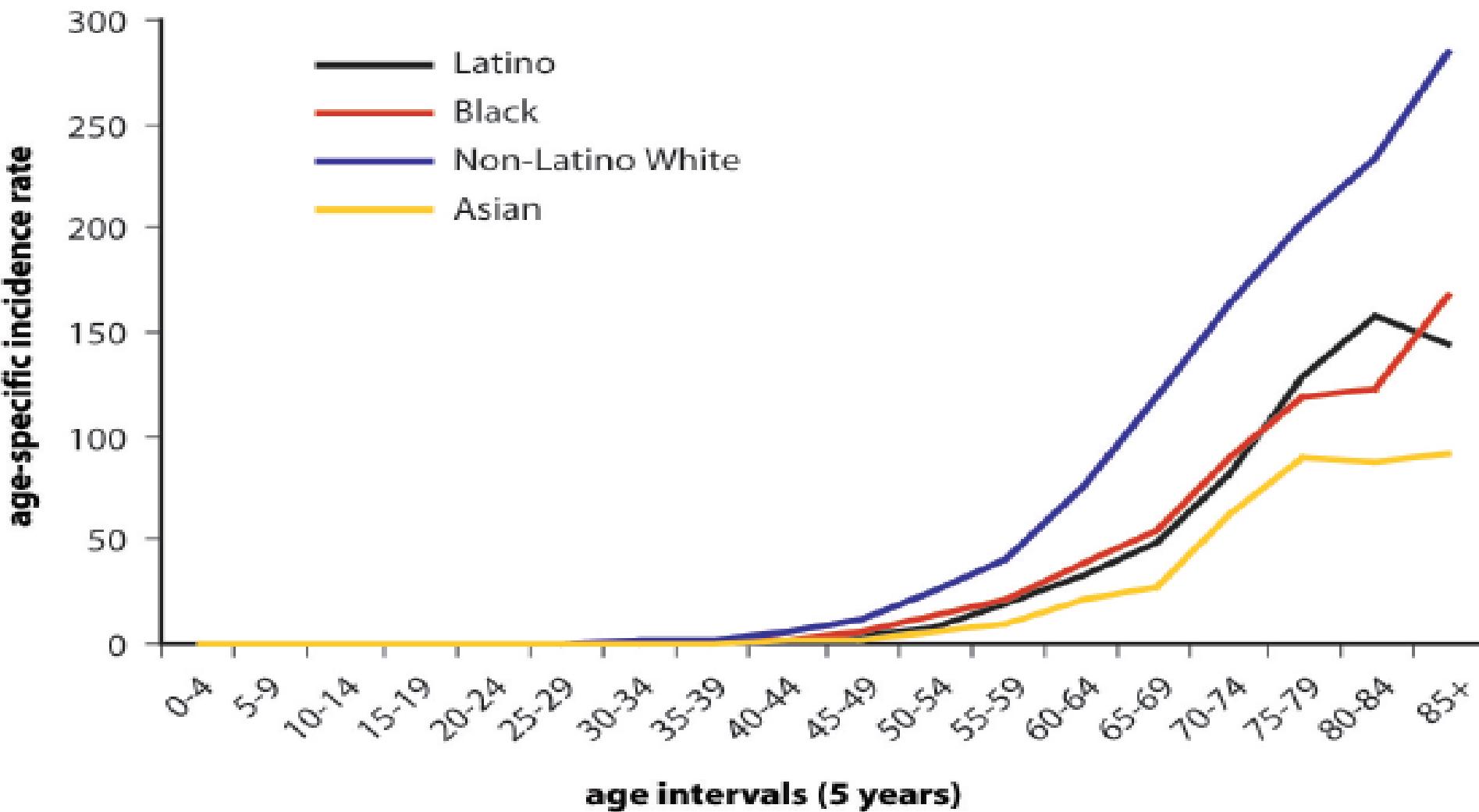
Female Lung Adenocarcinoma

Age-specific incidence by race/ethnicity (females)



Bladder Cancer

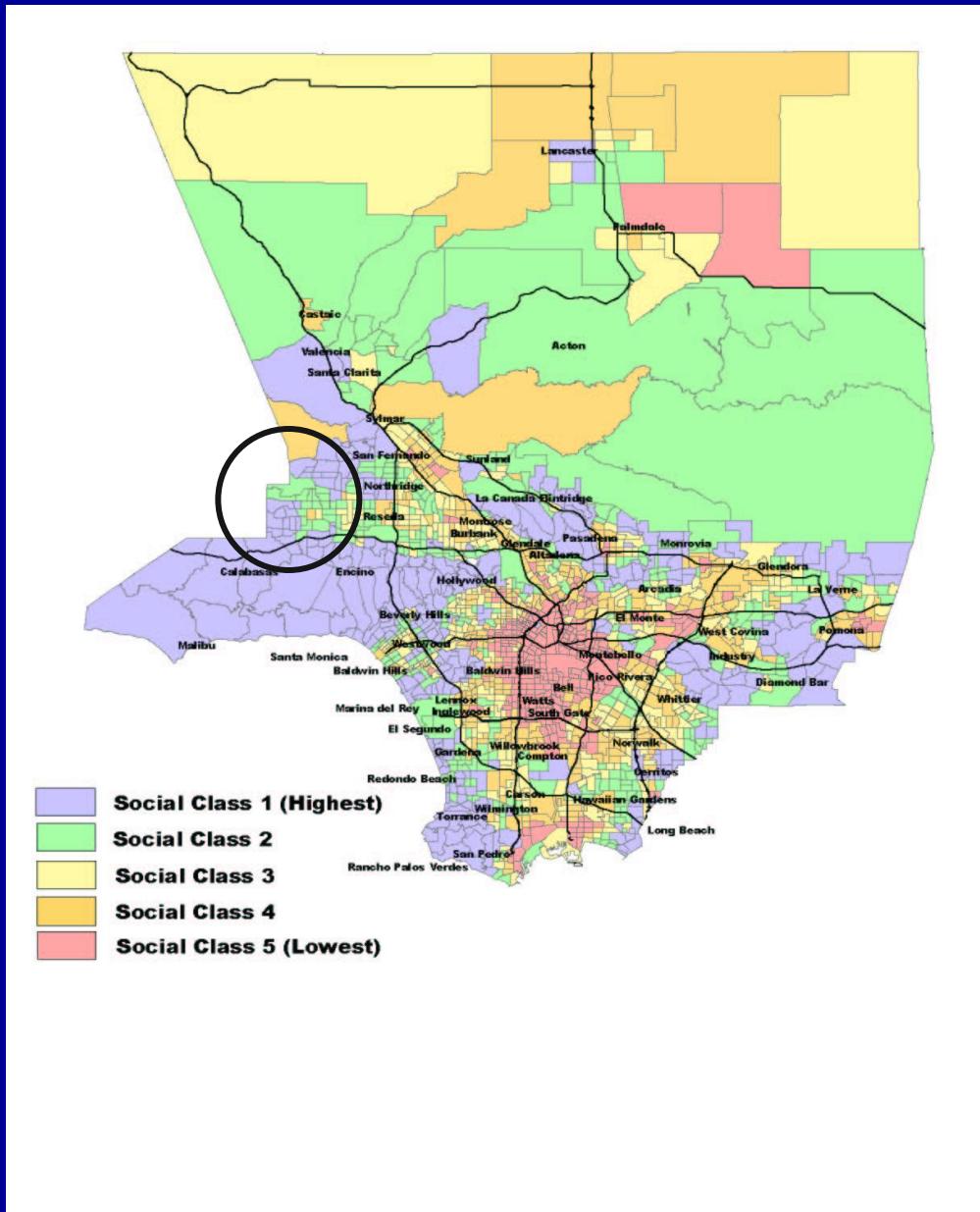
Age-specific incidence by race/ethnicity (males)



Other cancers higher in other Race/Ethnicity groups

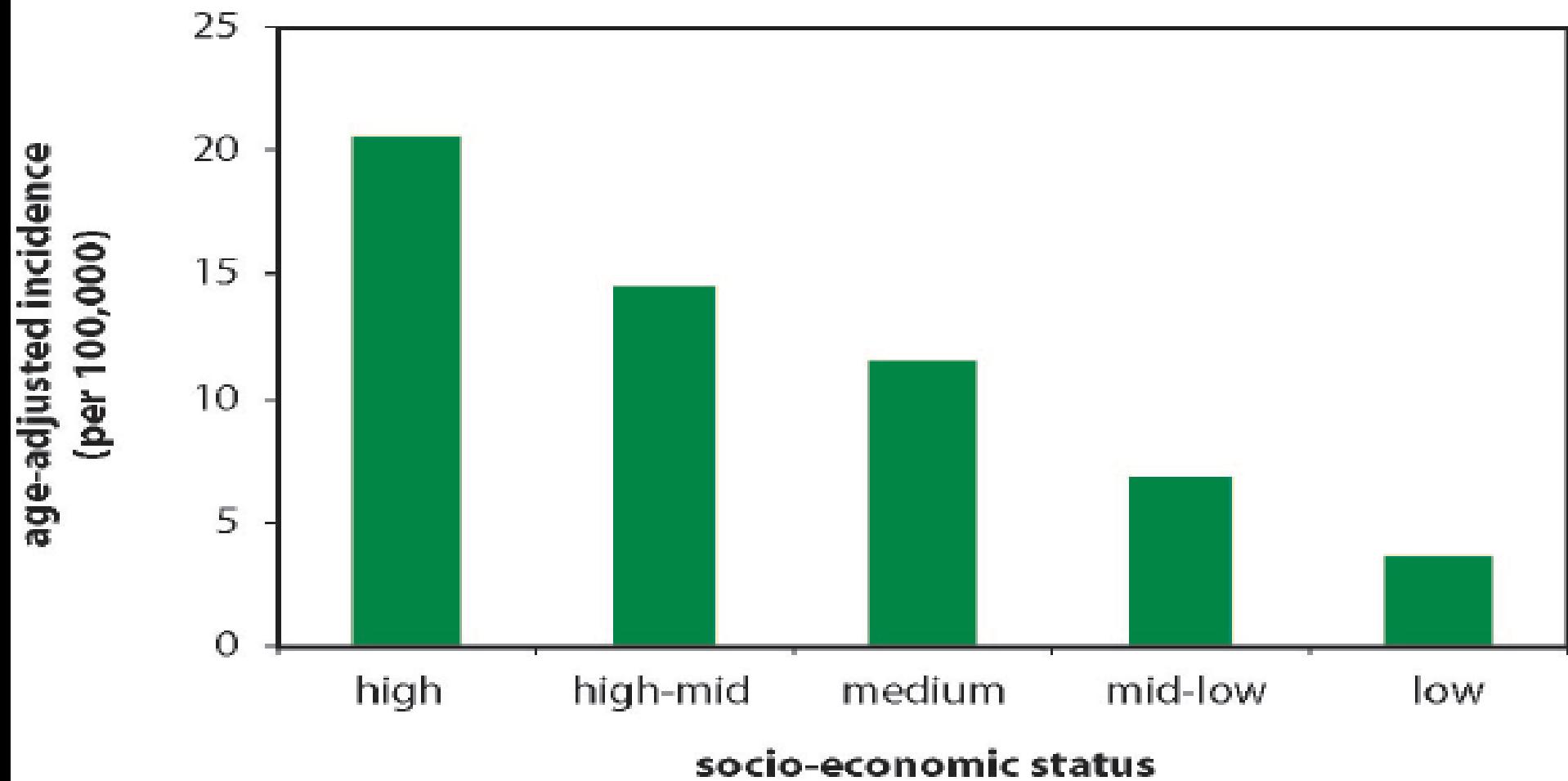
- Prostate cancer higher in African-Americans
- Liver cancer higher in East Asian-Americans
- Gall Bladder and stomach cancer higher in Latino-Americans

CENSUS TRACTS BY SOCIAL CLASS



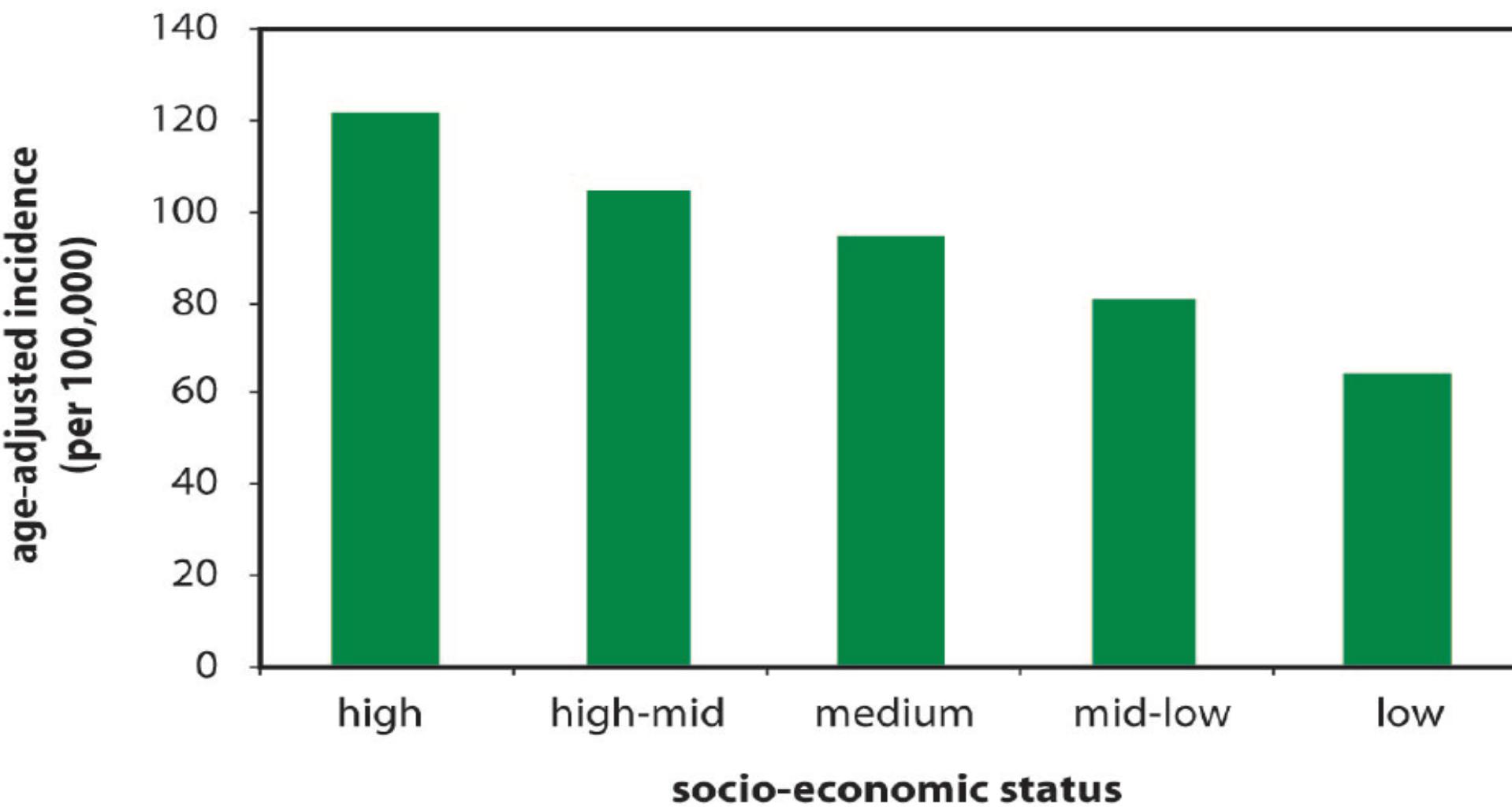
Malignant Melanoma

**Age-adjusted incidence by socio-economic status
(males)**



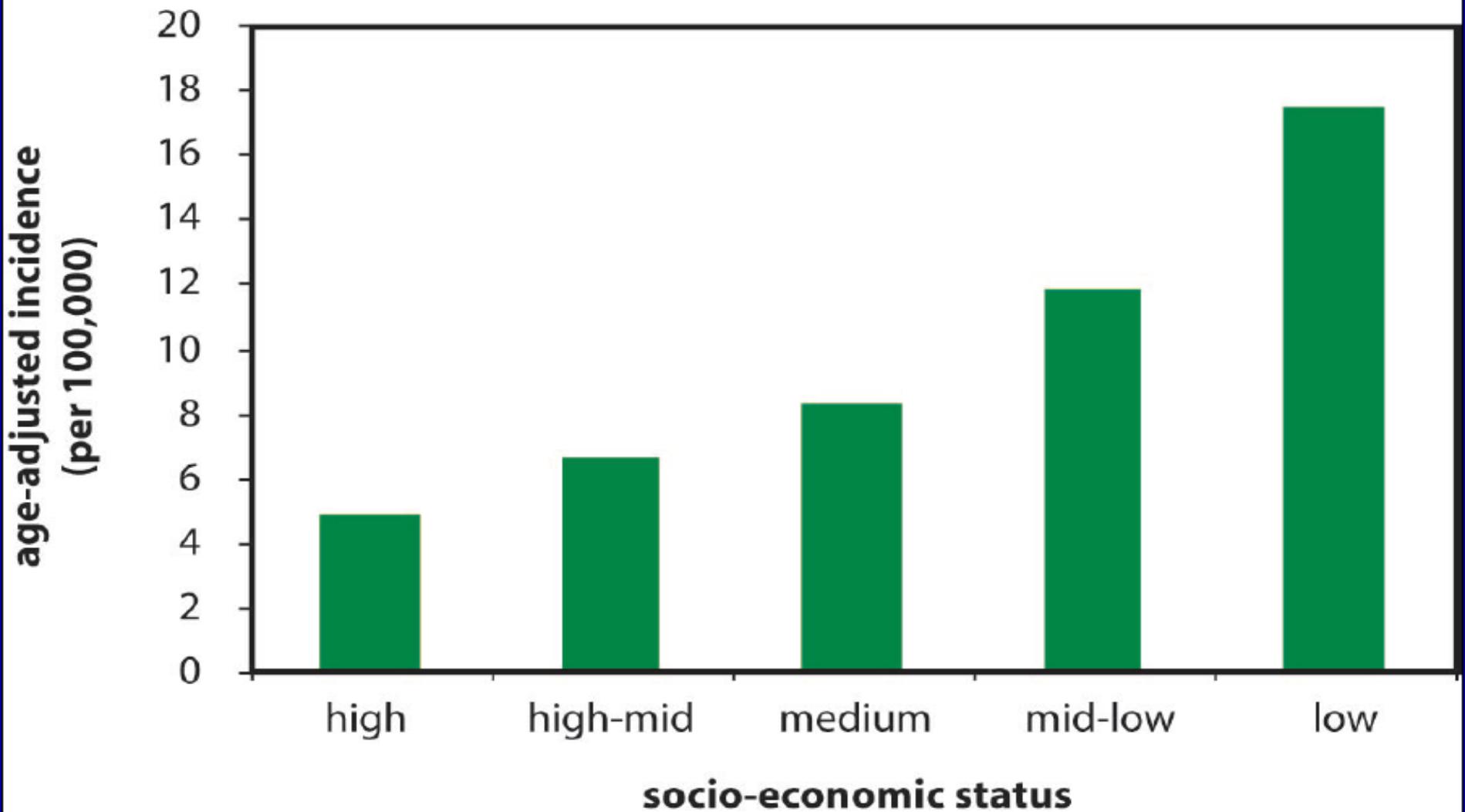
Female Breast Cancer

Age-adjusted incidence by socio-economic status (females)

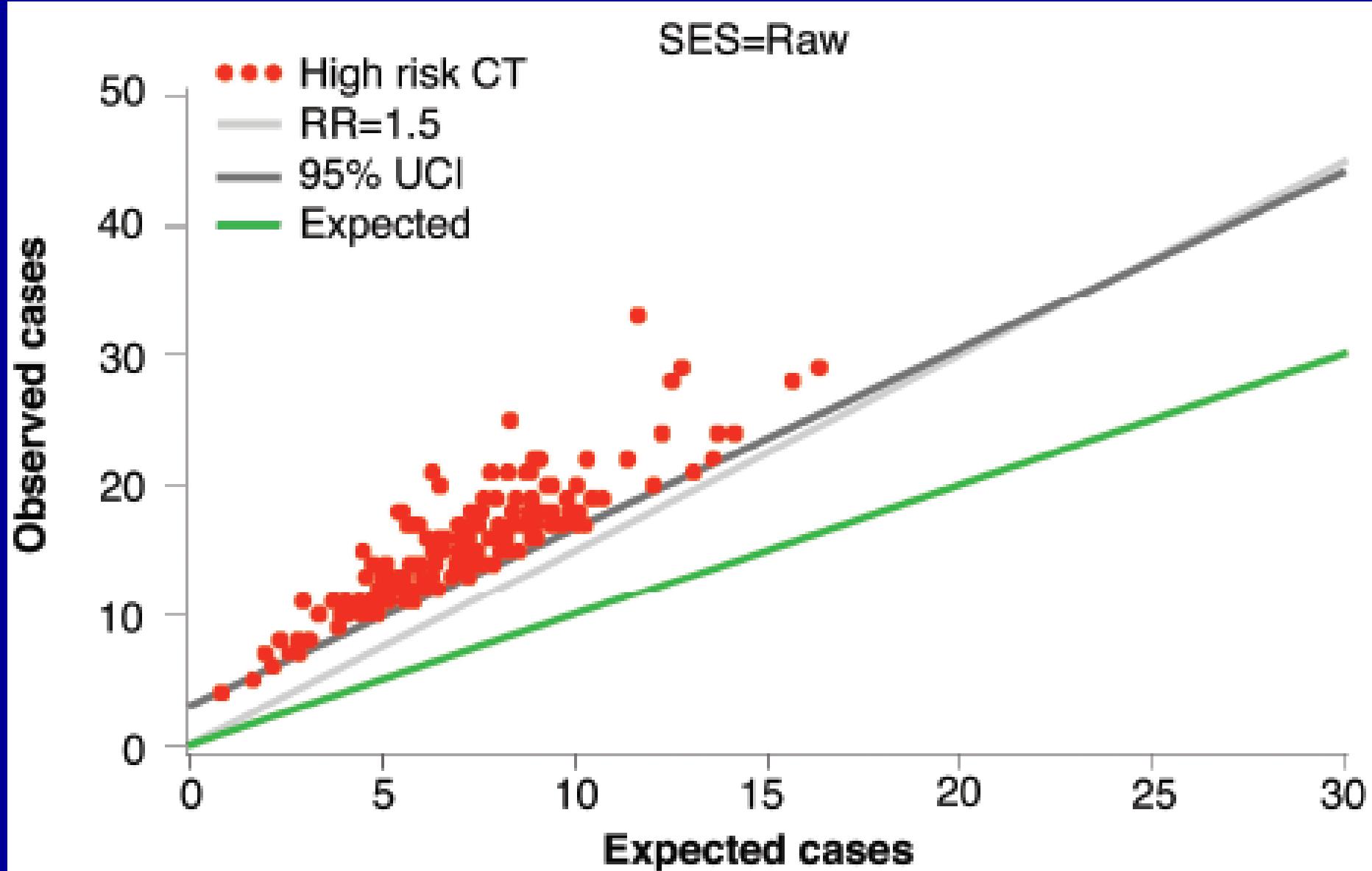


Cancer of the Cervix

Age-adjusted incidence by socio-economic status (females)

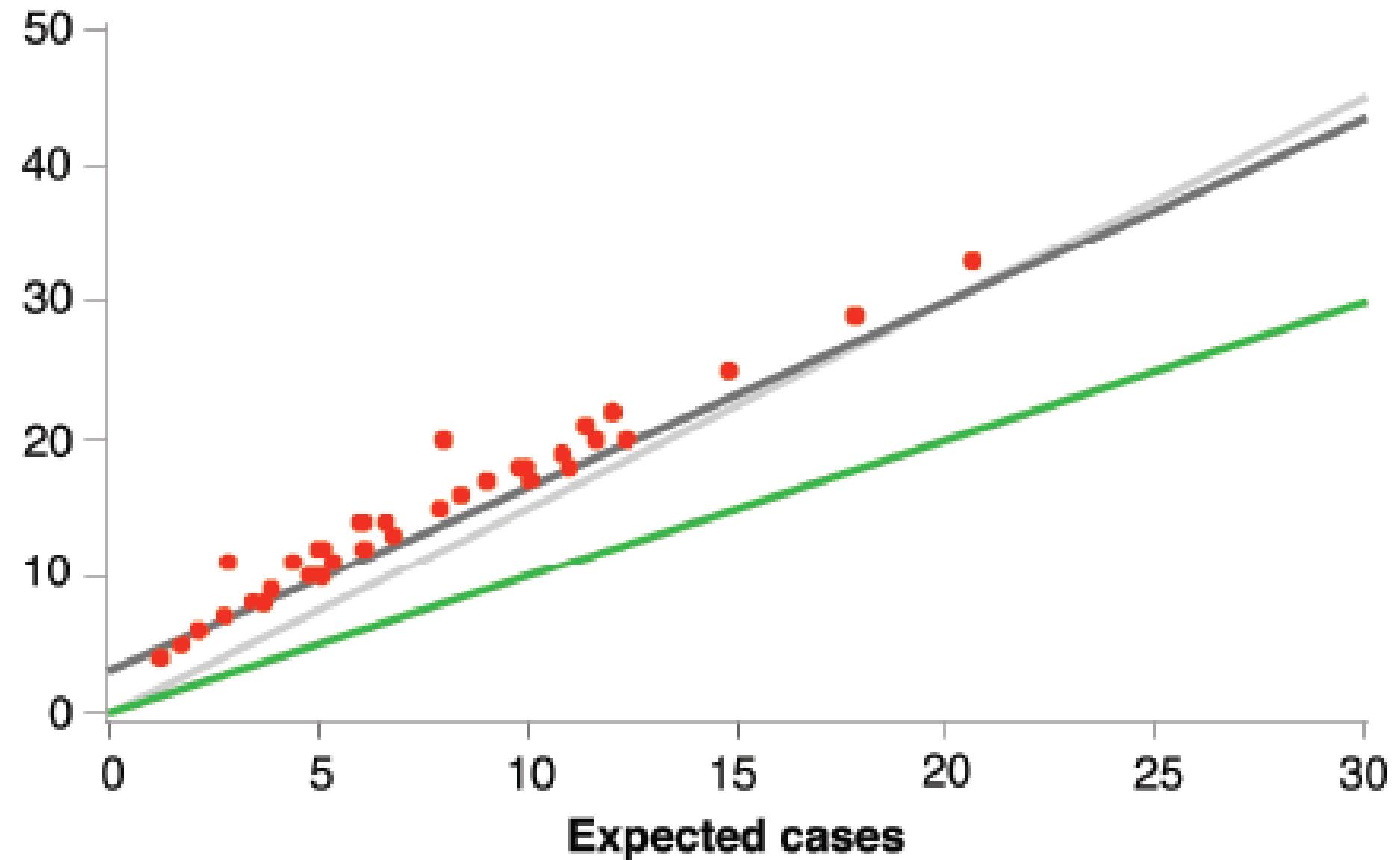


Female Cancer of the Cervix



Female Cancer of the Cervix

SES=Adj for SES



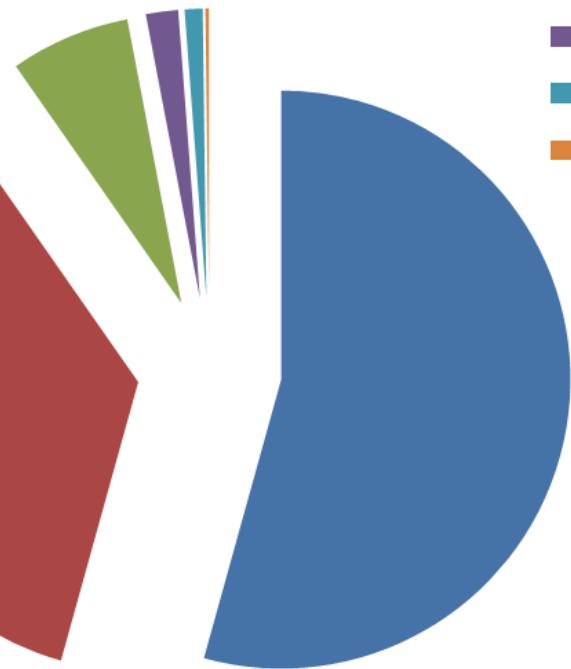
Cancers “cluster” for different reasons

- Lung cancer clusters by smoking, race, education
- Oropharynx cancer by smoking/drinking
- Cervical cancer by self/partner's sexual activity
- Kaposi sarcoma clustered by sexual preference
- Prostate cancer clusters by race, access to care
- Stomach cancer clusters by history of poverty
- Liver cancer clusters by parental ethnicity
- Thyroid cancer clusters by access to screening
- Mesothelioma clusters by occupation
- Melanoma clusters by race and education
- Breast cancer clusters by education/occupation

Characteristics of SSRL Offsite Tracts

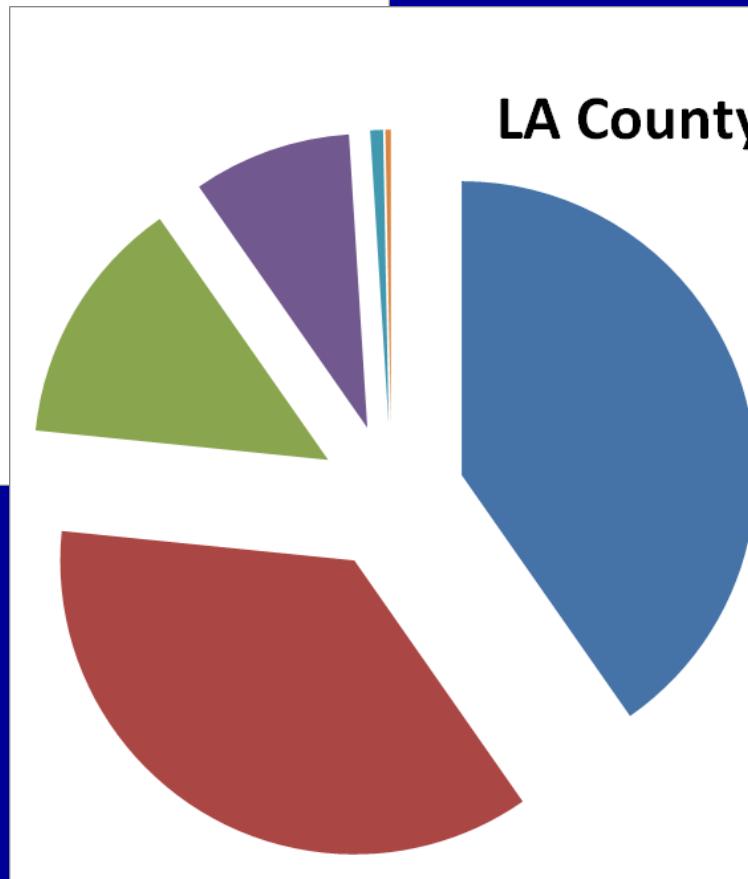
- They are not characteristic of their respective Counties in terms of:
 - Income and, doubtless, education
 - Race/ethnicity

Ventura County 2010



- European-American
- Latino-American
- Asian American
- African-American
- Native American
- Pacific Islander

LA County 2010

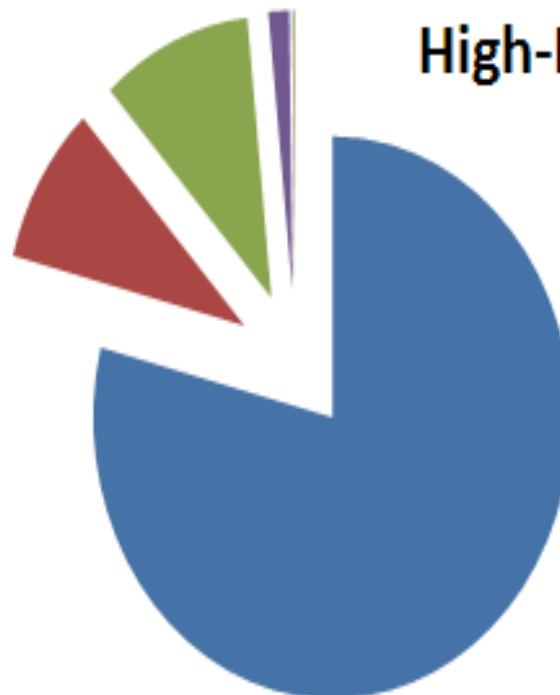


LA County High-Risk Tracts

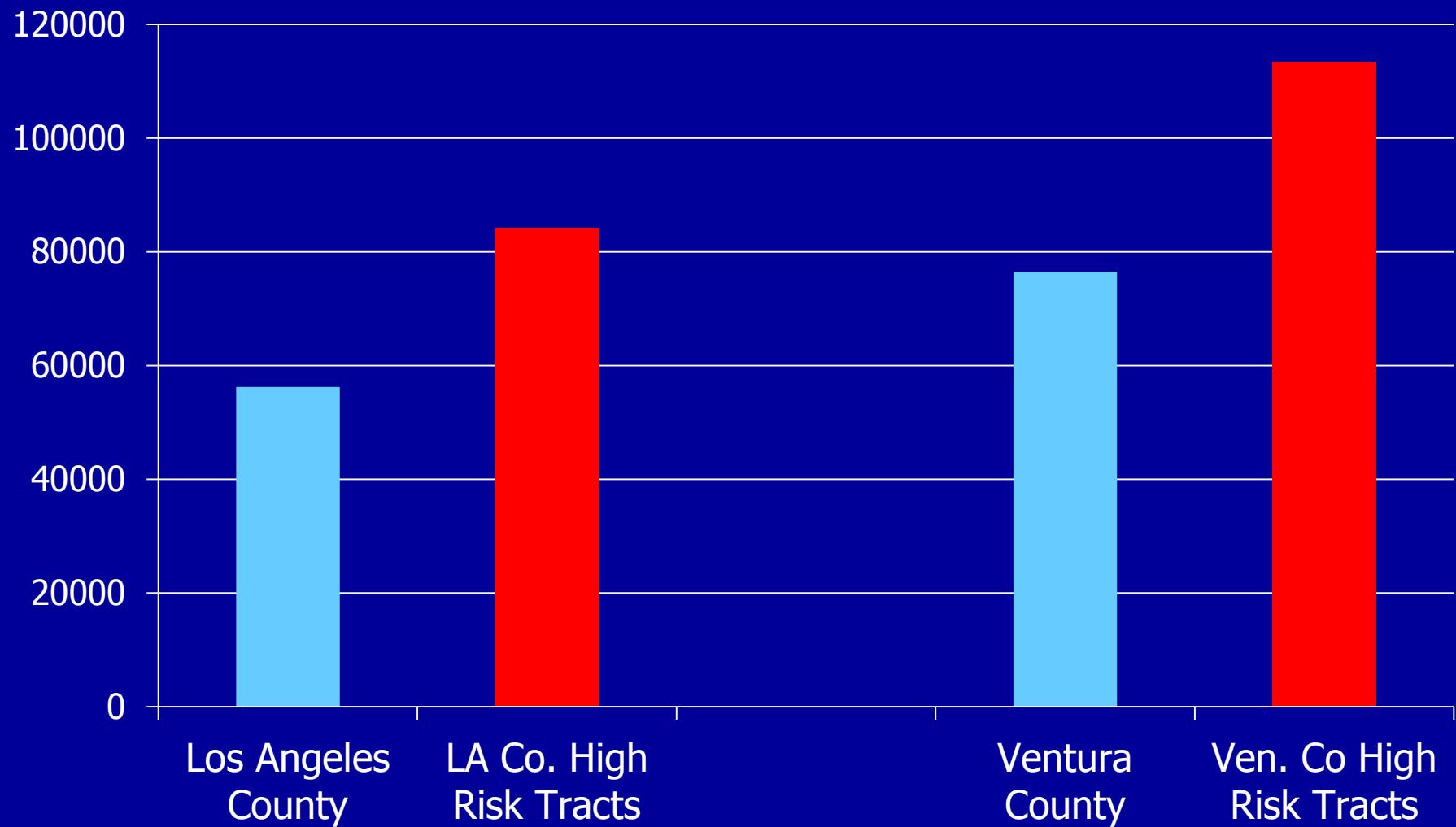


- European-American
- Latino-American
- Asian American
- African-American
- Native American
- Pacific Islander

Ventura County High-Risk Tracts



Median Family Income of Counties and of High Risk Tracts



From where do case reports come?

- Cancer reporting is mandatory since 1988
- California Cancer Registry covers the State
- All invasive malignancies (a few benign tumors)
- All cases found in a CA resident at diagnosis
- Hospitals collect reports to maintain certification
- Non-hospital labs, death certificates covered
- Reports returned to the place of residence
- Around 99% complete by regular audits using sampling and death certificates

Malignancies according to Annual (Age-Adjusted) New Cases /100,000

- **50+:** M Prostate, F Breast
- **30-49:** MF Lung, M/F Colorectum
- **10-29:** MF Melanoma, M Oropharynx, M Bladder, F Ovary, F Endometrium, MF Non-Hodgkin Lymphoma, M Leukemia
- **5-9:** M Stomach, M Larynx, M Testes, F Melanoma, F Thyroid
- F Cervix, F Oropharynx, F Leukemia, MF Pancreas, MF Kidney, MF Brain
- **<5:** M Thyroid, M Penis, F Stomach, F Larynx, F Bladder, MF Liver, MF Esophagus, MF Gallbladder, MF Hodgkin Lymphoma, MF Eye

Selection of malignancies

- Every cancer has a unique set of causes
 - (A few exposures, i.e. smoking, cause a portion of several cancers, but the rate of cancer at all sites is not informative)
- Cancers were selected for assessment:
- In all, thirteen different malignancies
 - The four most common cancers
 - Others possibly caused by chemicals/radiation

Cancers selected

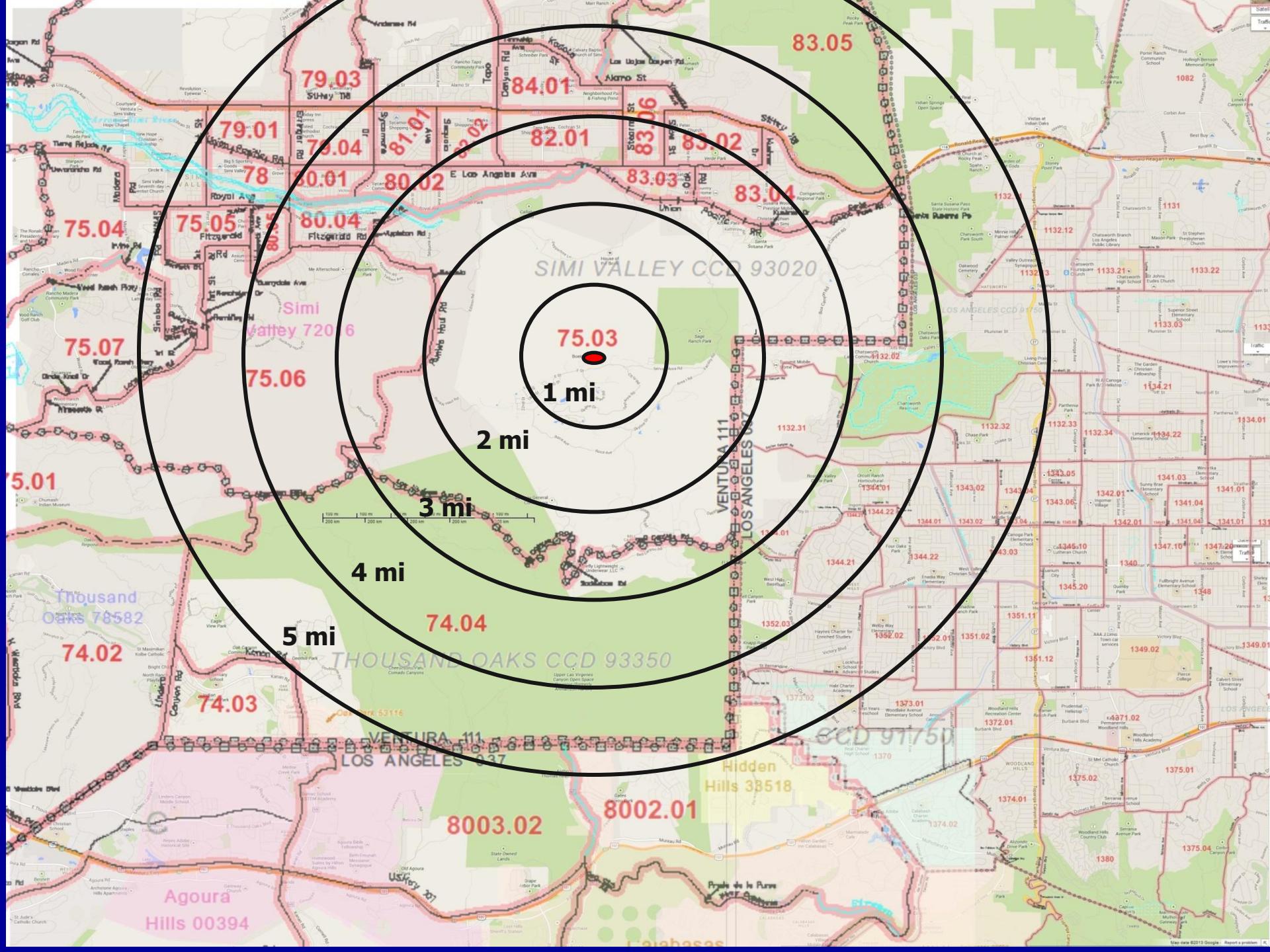
Neoplasm	Major Causes	Descriptive Predictors
Lung	Cigarette smoking	Blue collar occupation
Bladder	Cigarettes, aniline dyes (rare)	White Race
Pancreas	Cigarette smoking	None strong
Oropharynx	Tobacco, Alcohol, Pap.Virus	None strong
Leukemia	Genes, benzene, ? virus	None strong
Breast	Genes, Hormones	Higher education
Colorectal	Genes, Diet, Activity	None strong
Prostate	Genes, Diet	Race, Age, Access to screening
Thyroid	Ionizing radiation (rare)	Access to screening
Brain	Ionizing Radiation (rare)	None strong
Liver	Hepatitis B, C viruses	National origin
NHL	Immune depletion	None strong
Melanoma	Sunlight, light skin	Race, Higher education

Screening Methods

- Genders assessed separately
- Three time periods:
 - 1988-95, 1996-2003, 2004-2010
 - Separate denominators from 3 censuses
- All census tracts within 5 miles of SSFL
 - 1988-95: 22 VEN, 16 LA census tracts
 - 1996-2003 : 29 VEN, 17 LA census tracts
 - 2004-2010: 29 VEN, 17 LA census tracts
- Number of comparisons:
 - 130 period-tracts X 24 gender-cancers= 3120 searches
 - Up to 78 (3 per gender-cancer) “significantly” high-risk tracts by chance

Screening Criteria

- Significantly higher rate than County mean at the 95% confidence level ($p < 0.05$)
- At least a 50% increase in risk ($RR > 1,5$)
- Histological (Causal) homogeneity of excess



To find a result consistent with local cancer causation by disbursed carcinogen

- Consistent risk over calendar time
- High risk for both genders in the same area
- Higher risk proximate to SSRL
- Geographic clustering of high risk areas
- Pattern consistent with dispersion flow
- We screen by a relative risk (RR) of 1.5, but if RR is below 2.0, any observed case would likely have occurred anyway
- No plausible alternative explanation is available

Reasons for Caution in Assessing Impact

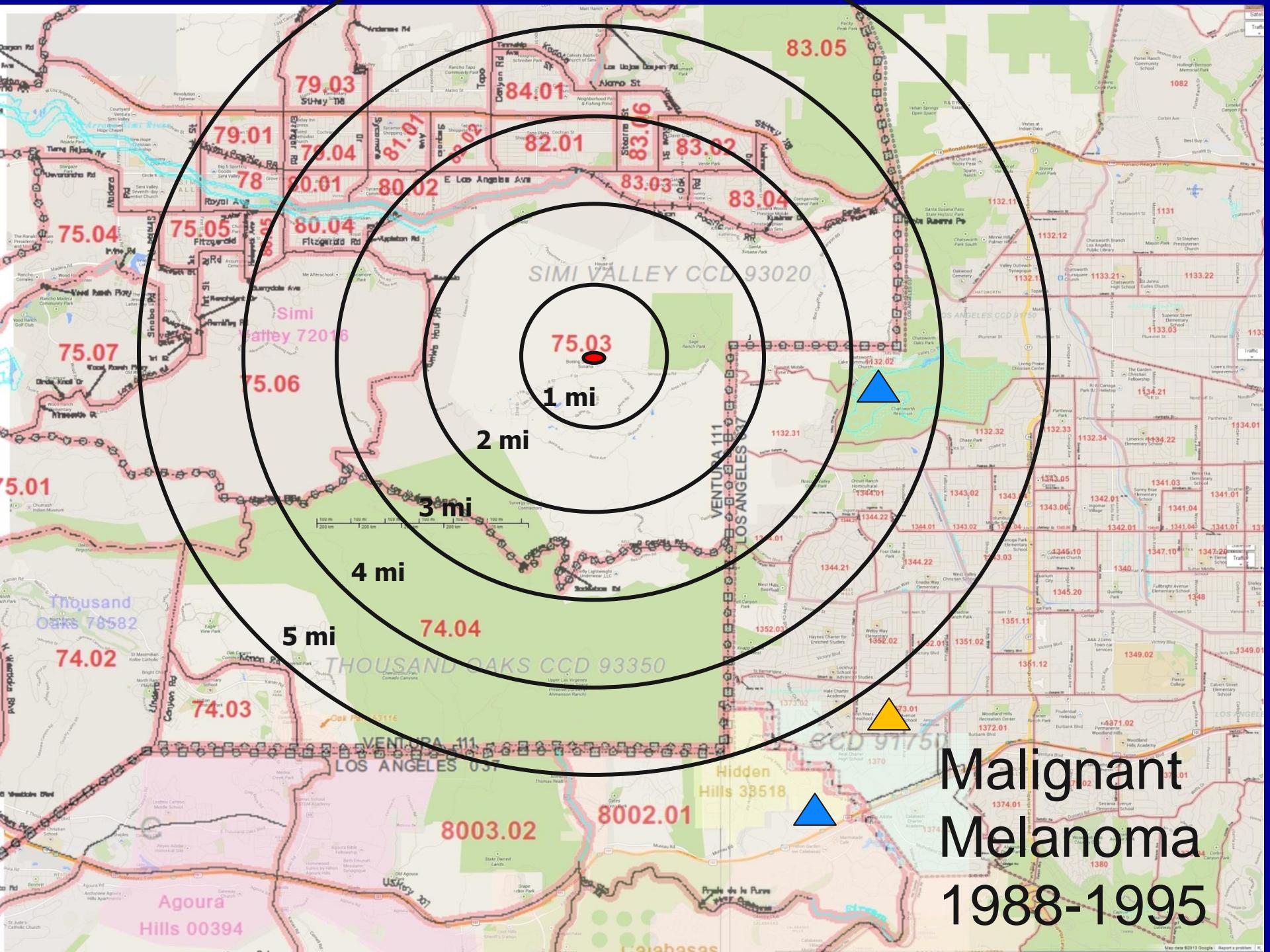
- 3 “Significant” excesses each are expected by chance
- No known clear evidence of personal exposure
- Waterborne and airborne dispersion imprecise
- Dosage is unknown
- Exposed workers are likely to reside together
- Census errors: rapid local growth may distort incidence estimates
- Evaluation is based on residential address at diagnosis

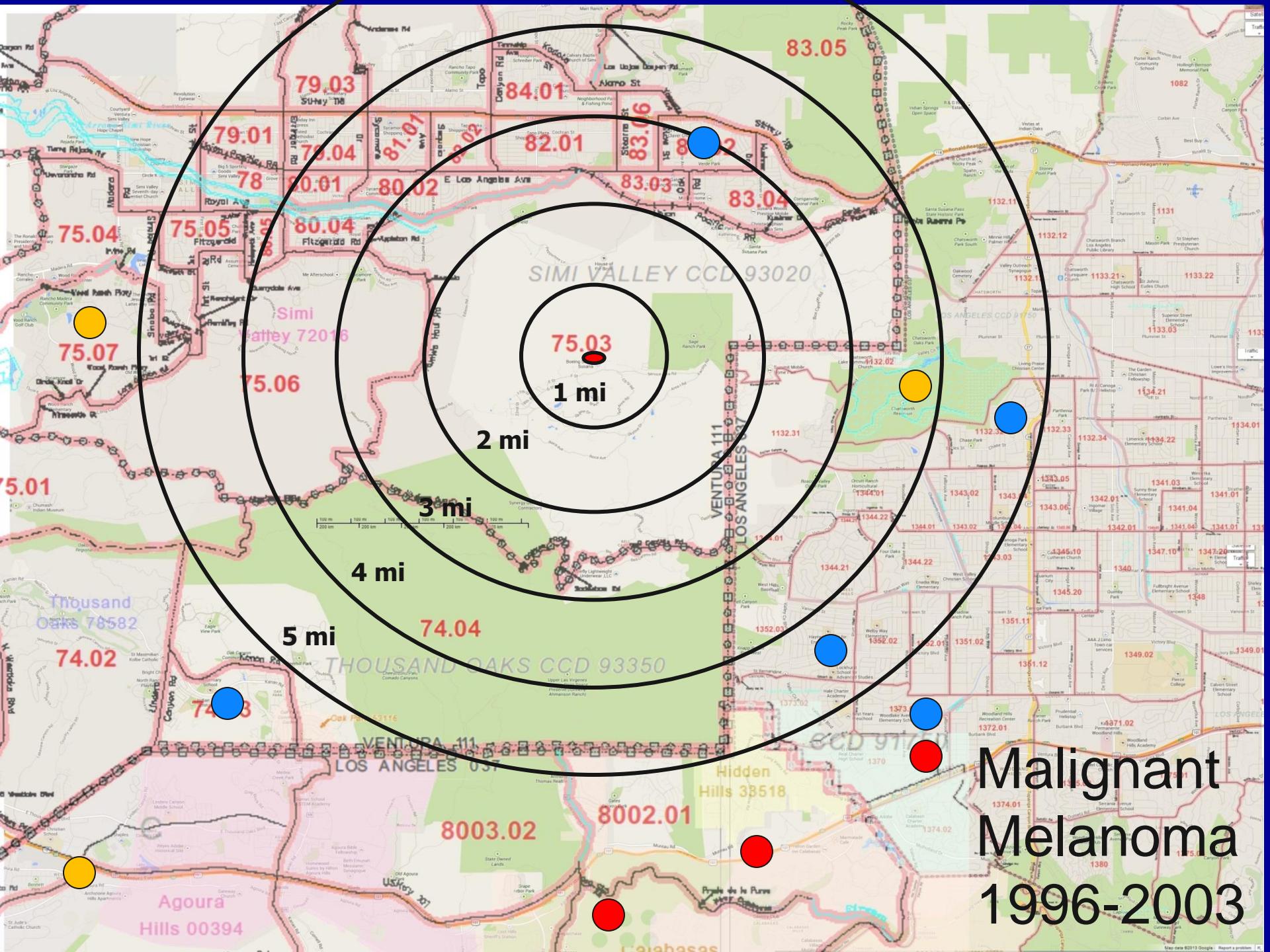
Summary Screening Findings

Neoplasm	“Significant” tract-periods	In Both genders	In Adjacent tracts	In 2 or more periods
Breast	26 (3 exp)	---	8	6
Melanoma	23 (6 exp)	8	17	7
Colorectal	7 (6 exp)	2	0	0
Lung	4 (6 exp)	0	0	1
Prostate	4 (3 exp)	---	0	0
Thyroid	3 (6 exp)	0	0	0
Brain	3 (6 exp)	0	0	0
NHL	2 (6 exp)	0	0	0
Leukemia	1 (6 exp)	---	---	--
Bladder	1 (6 exp)	---	---	---
Oropharynx	0 (6 exp)	---	---	---
Liver	0 (6 exp)	---	---	---
Pancreas	0 (6 exp)	---	---	---

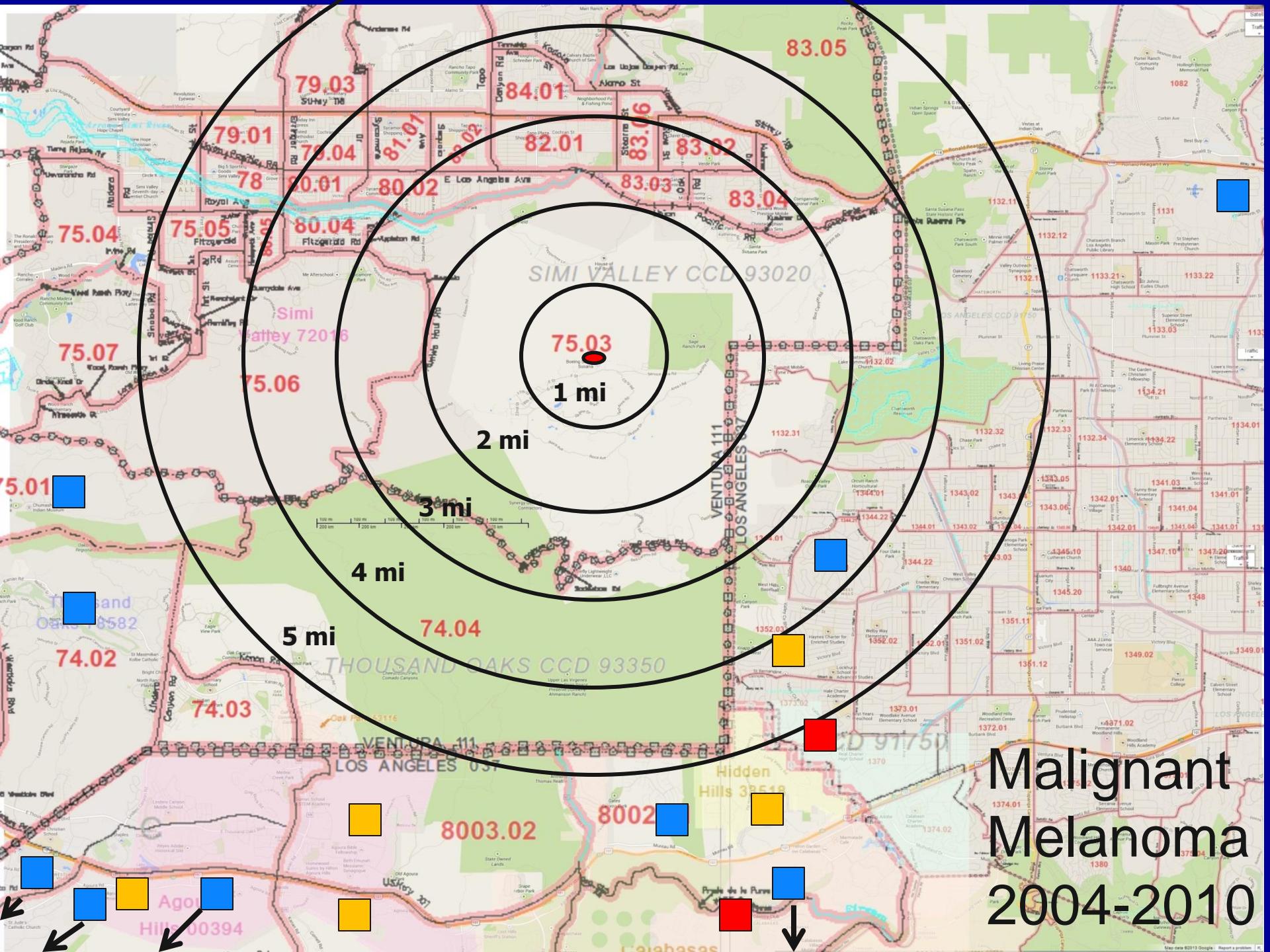
Legend

Period	Males	Females	Both
1988-1995			
1996-2003			
2004-2010			

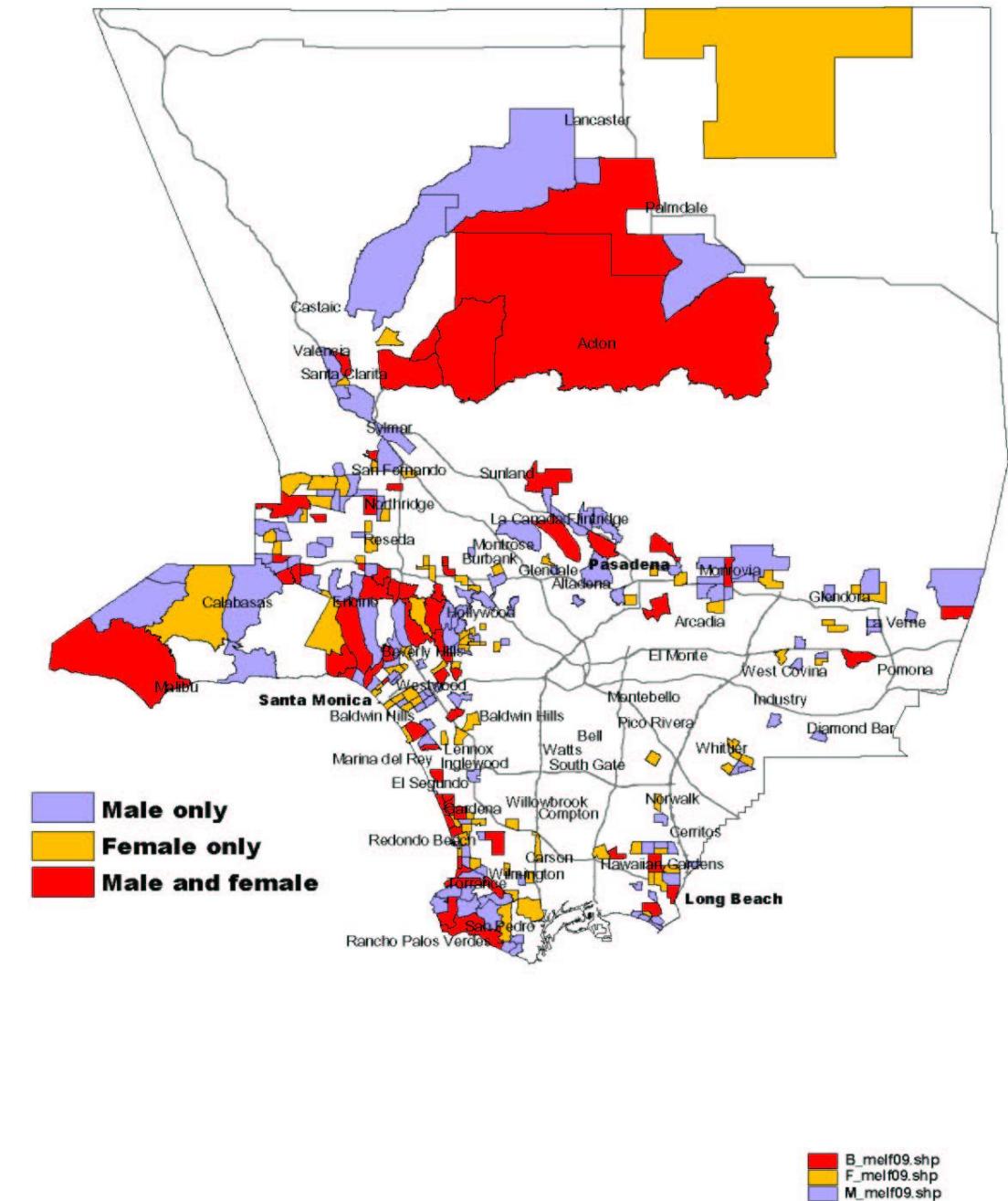




Malignant Melanoma 1996-2003

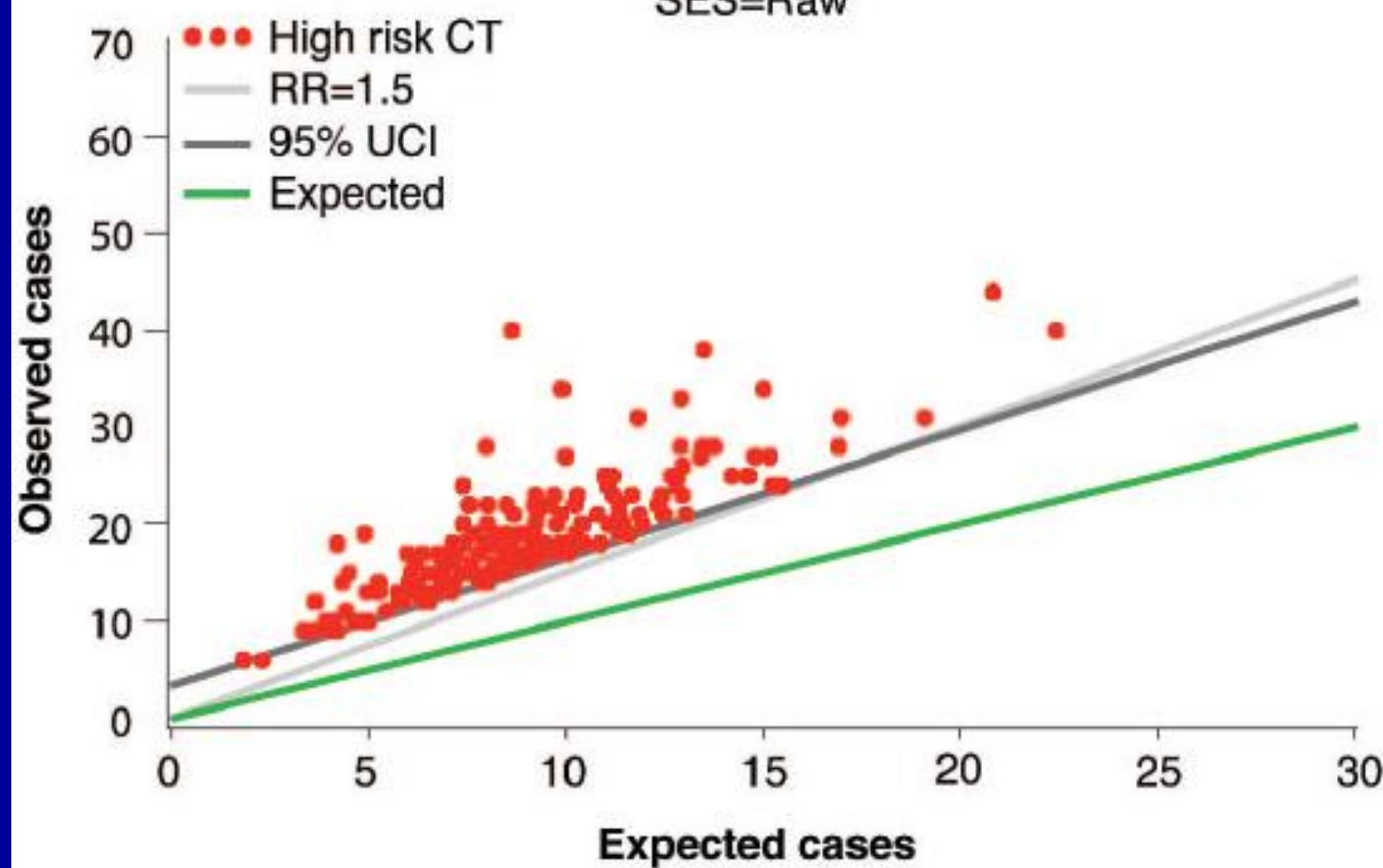


Malignant Melanoma



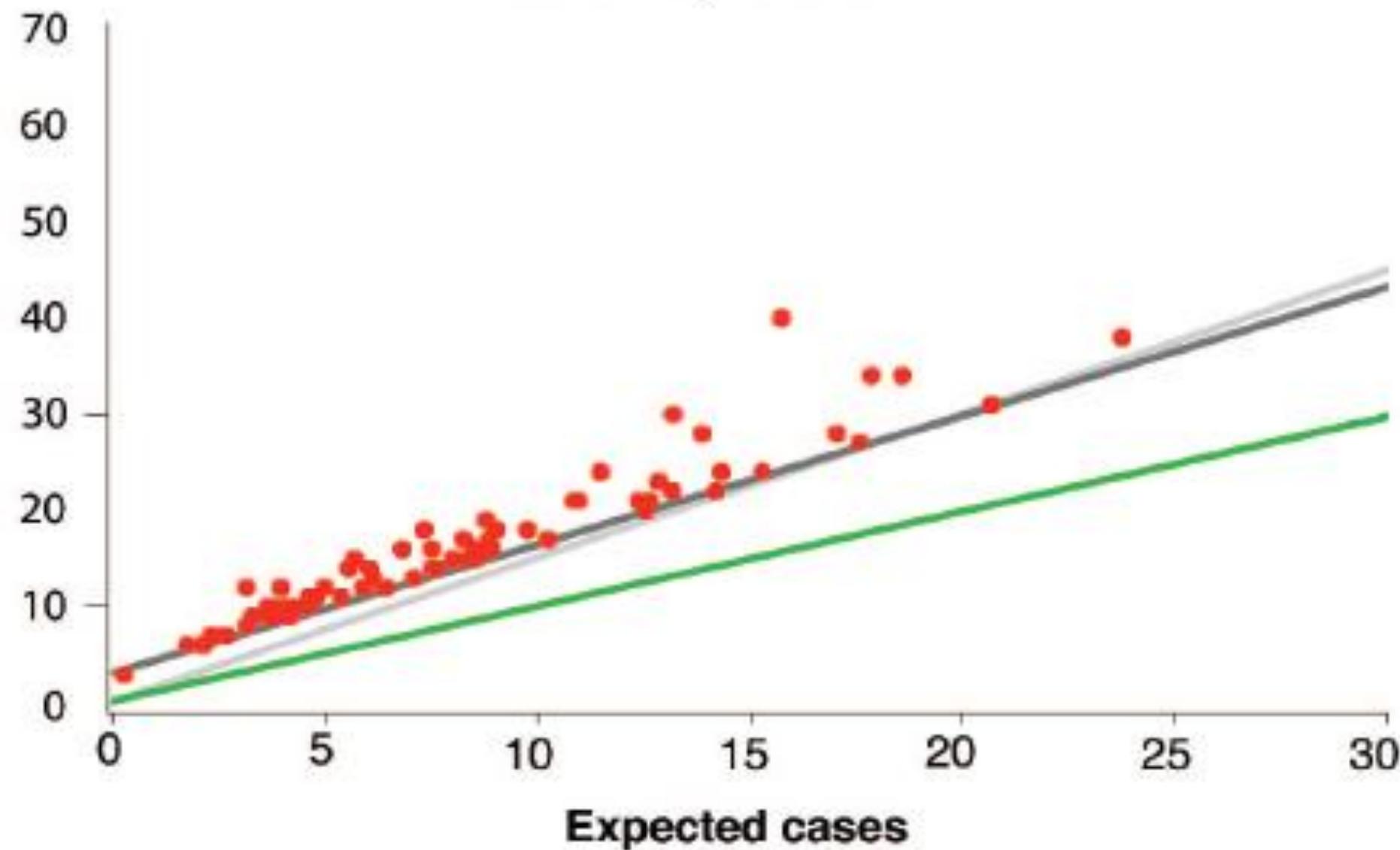
Malignant Melanoma

SES=Raw

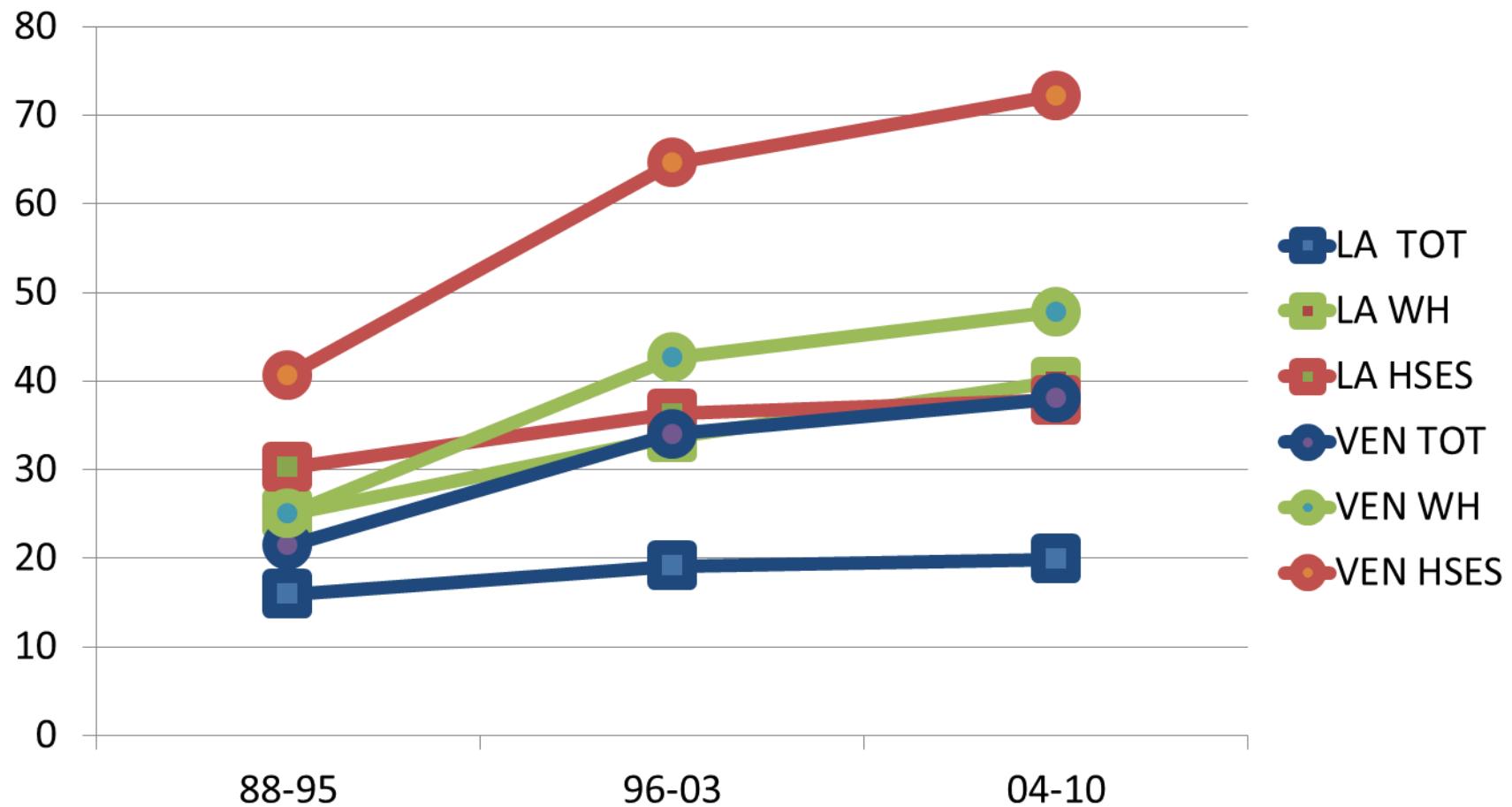


Malignant Melanoma-Adjusted for SES

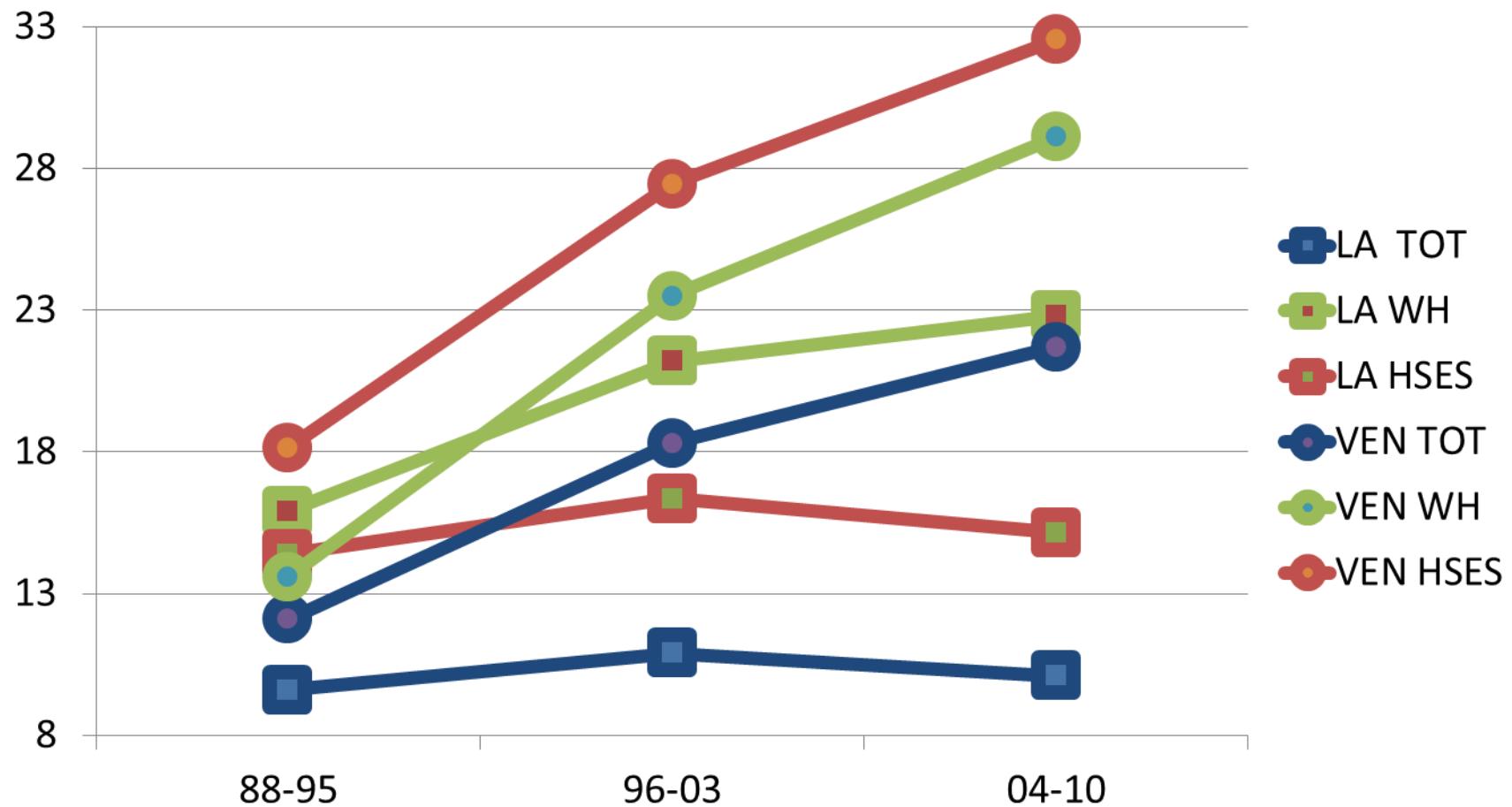
SES=Adj for SES

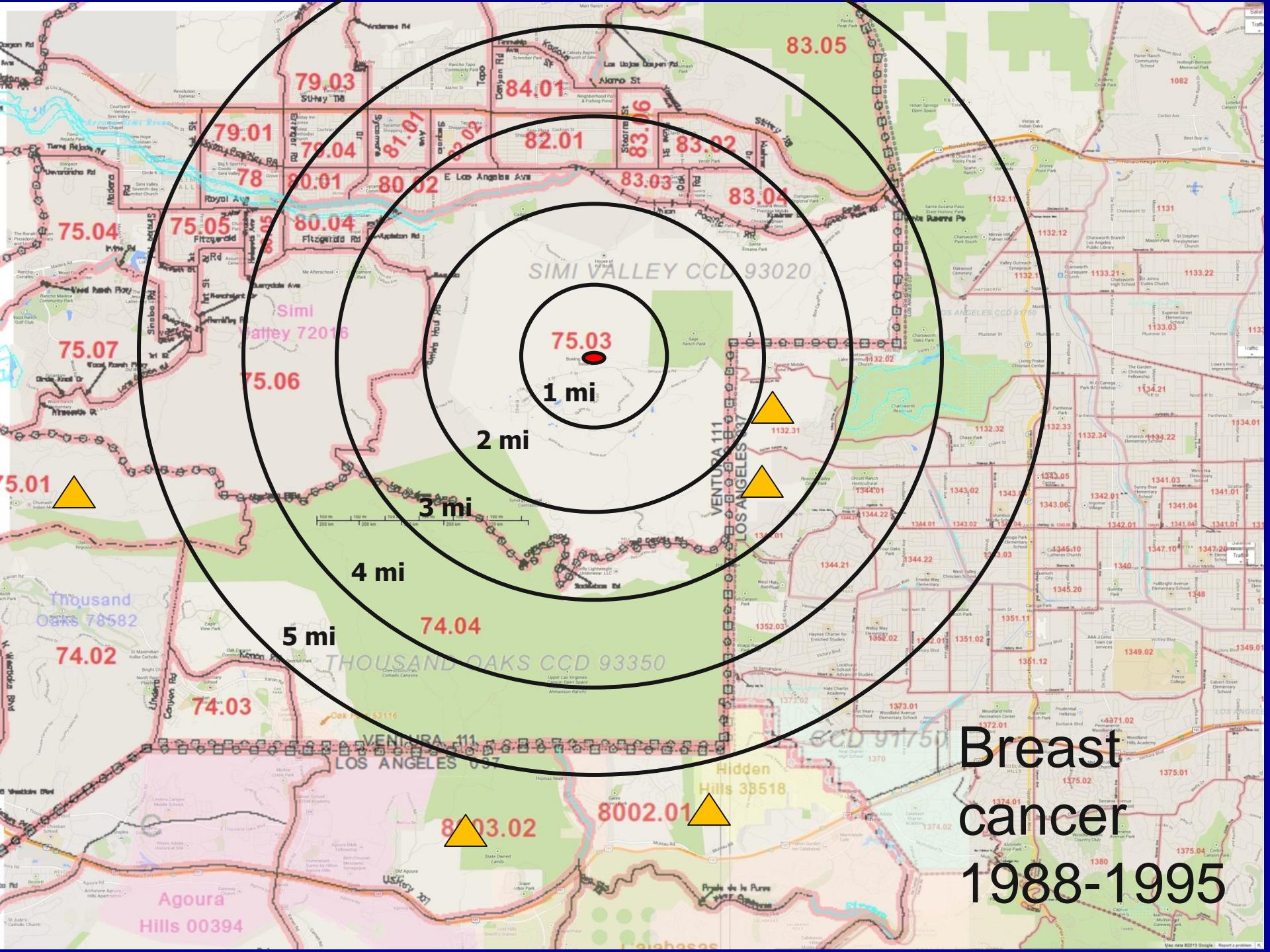


MALE MELANOMA



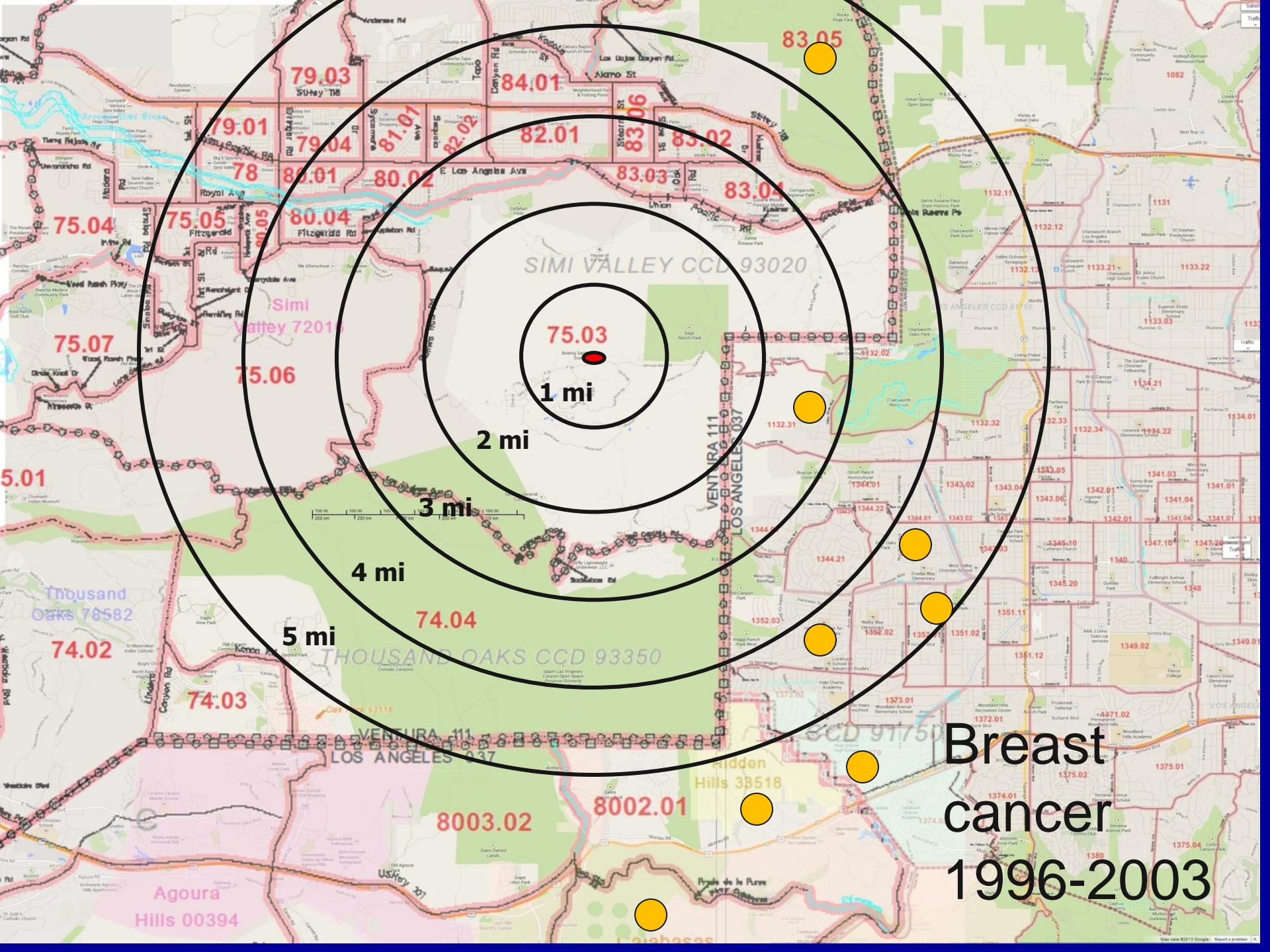
FEMALE MELANOMA

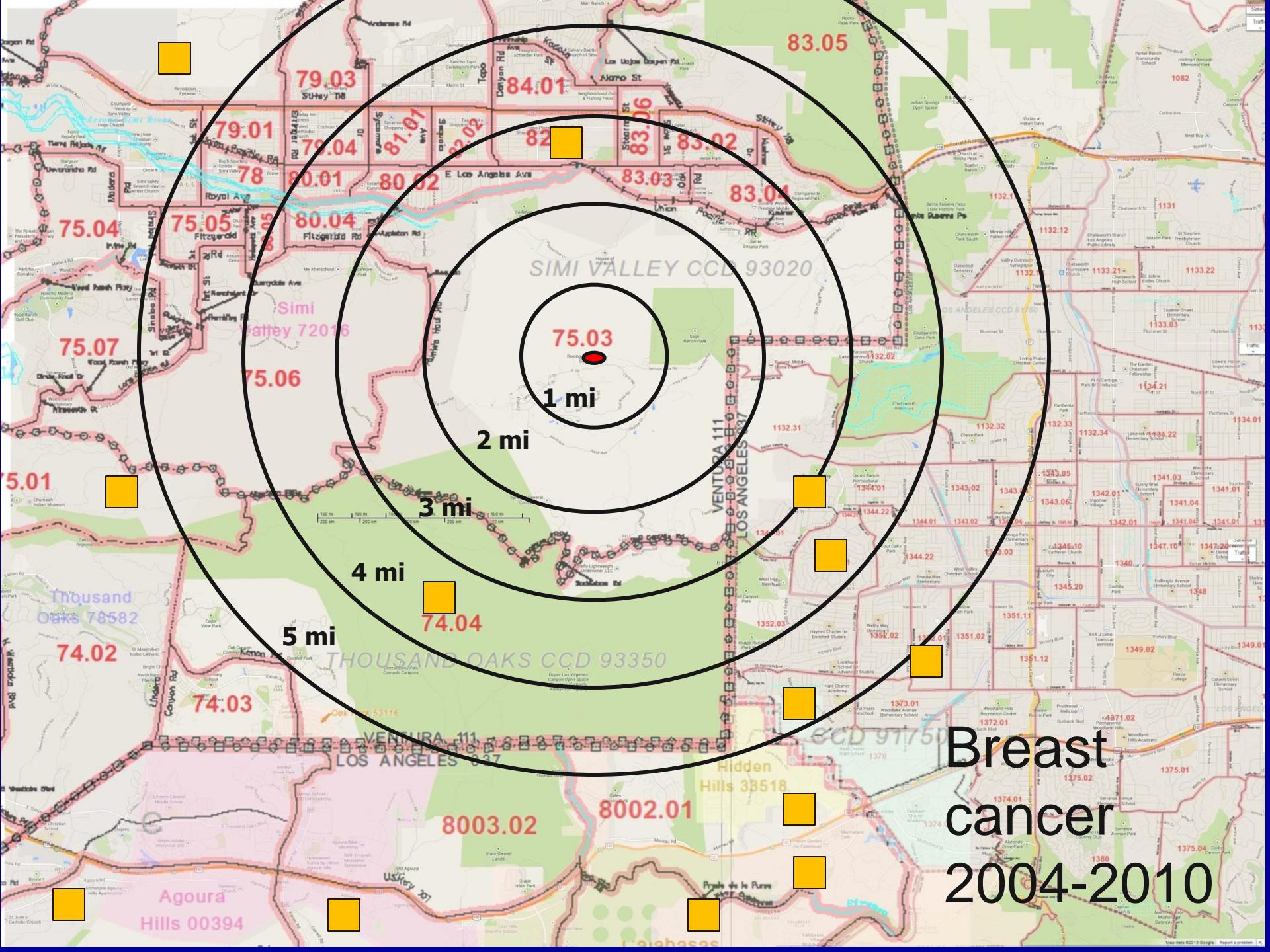




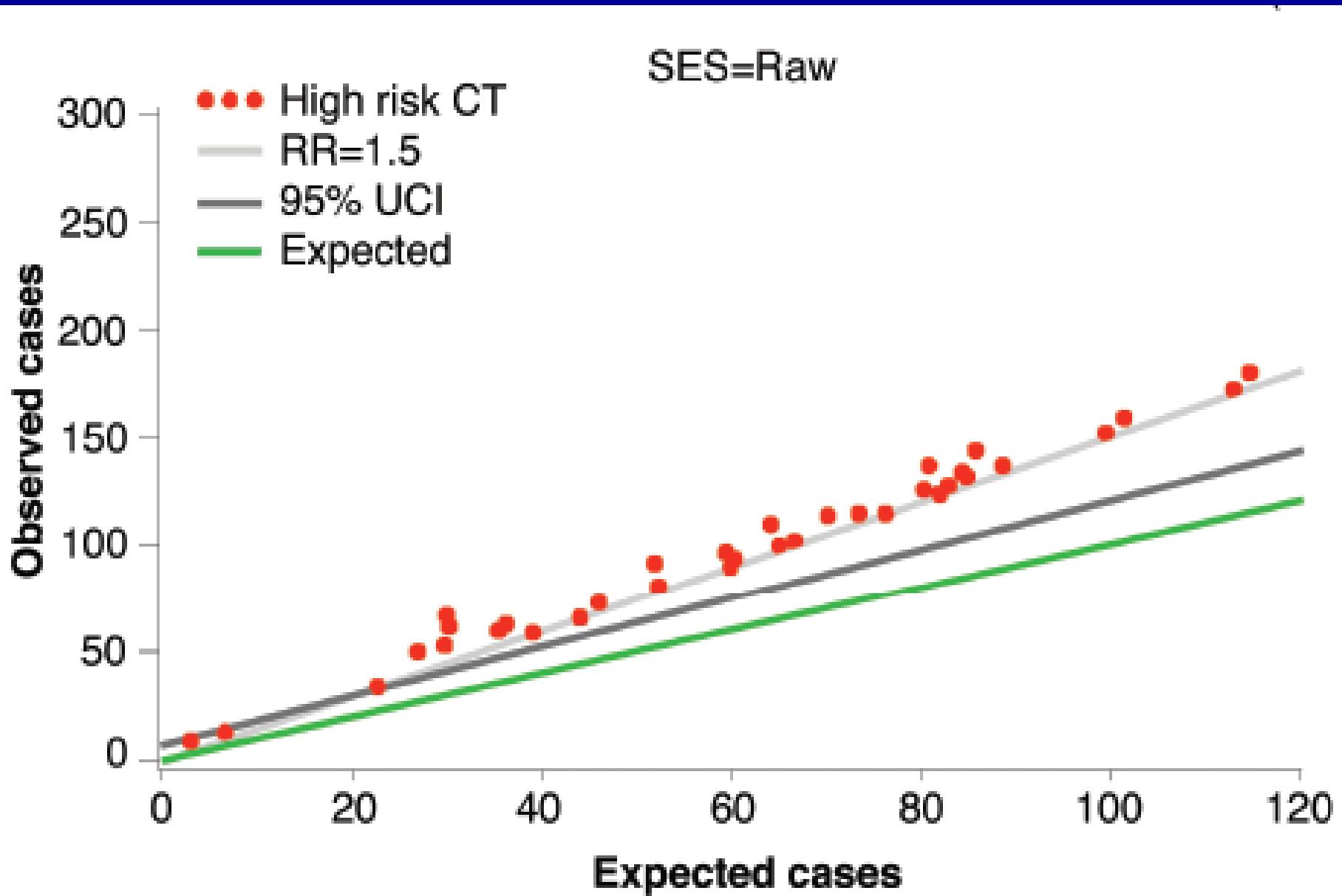
Breast cancer 1988-1995

Breast cancer 1996-2003



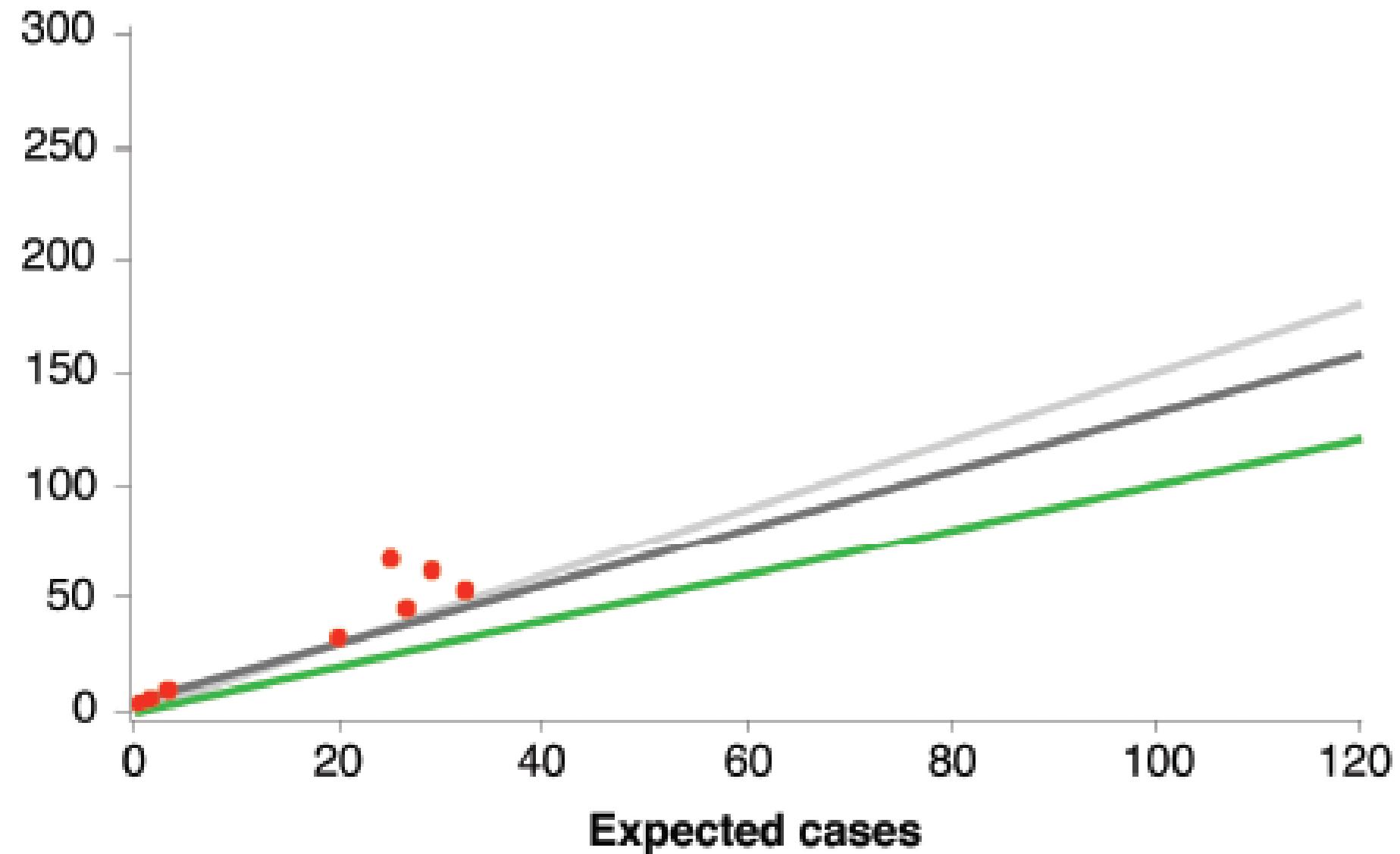


Female Breast Cancer

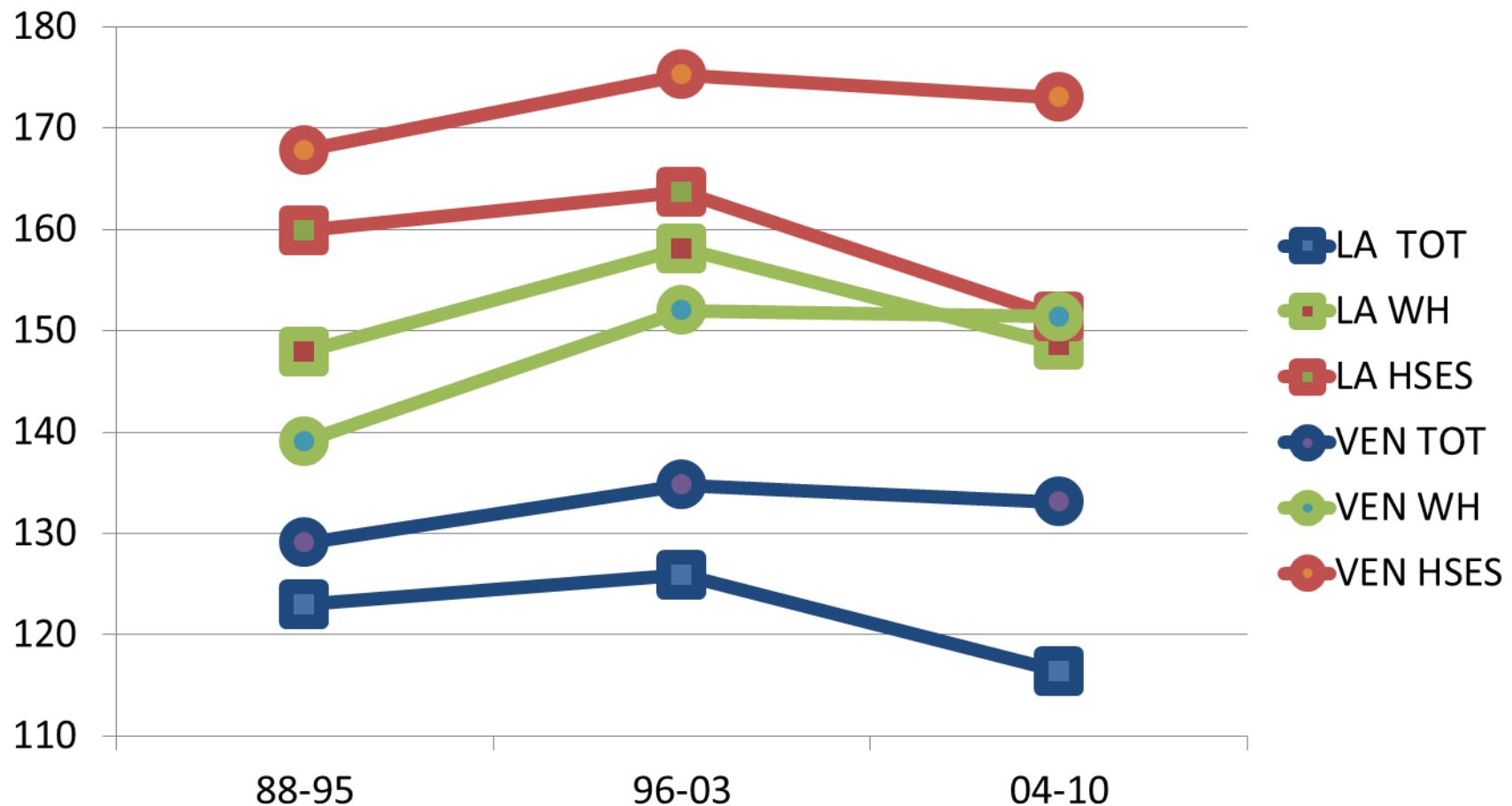


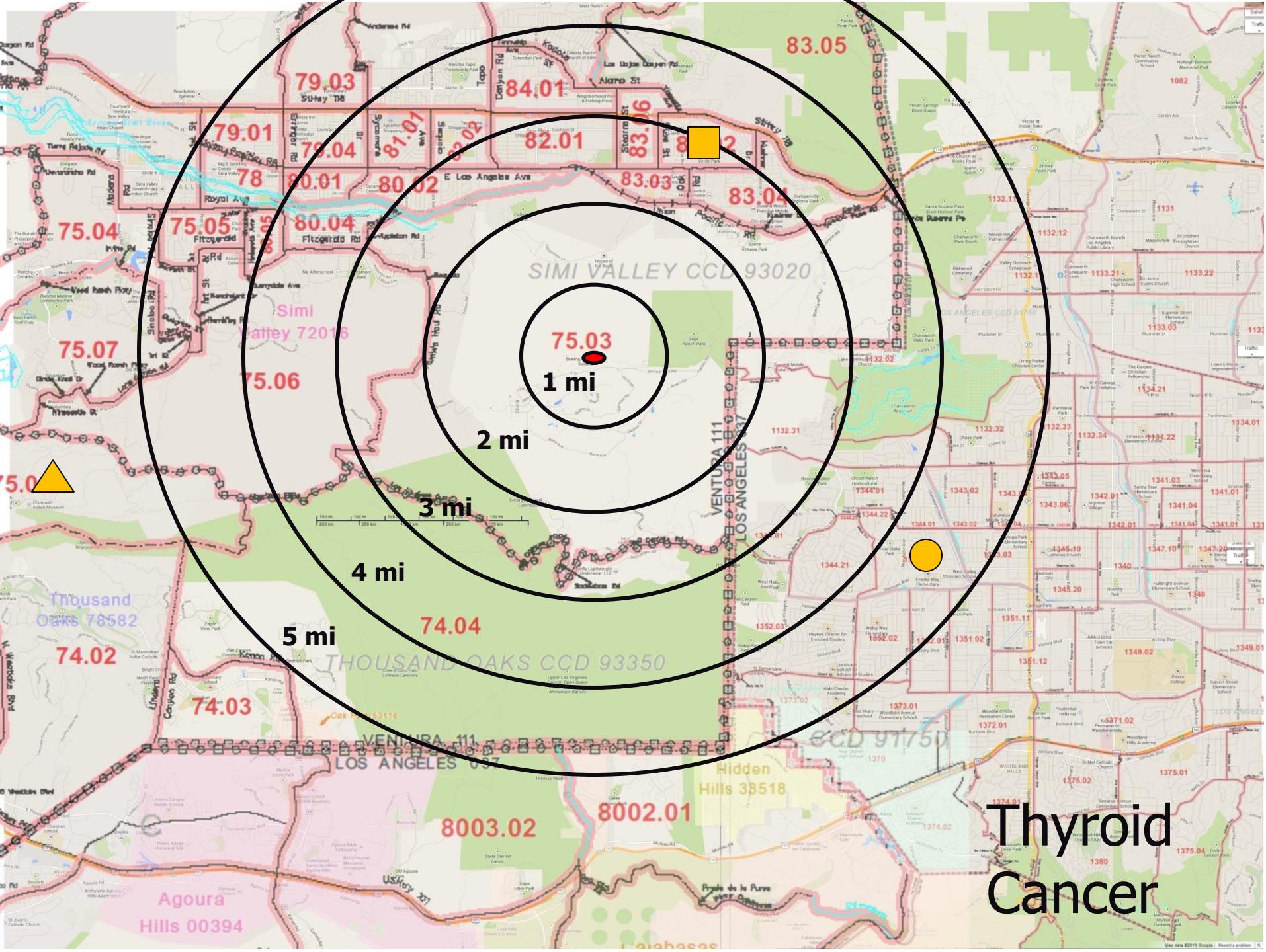
Female Breast Cancer

SES=Adj for SES



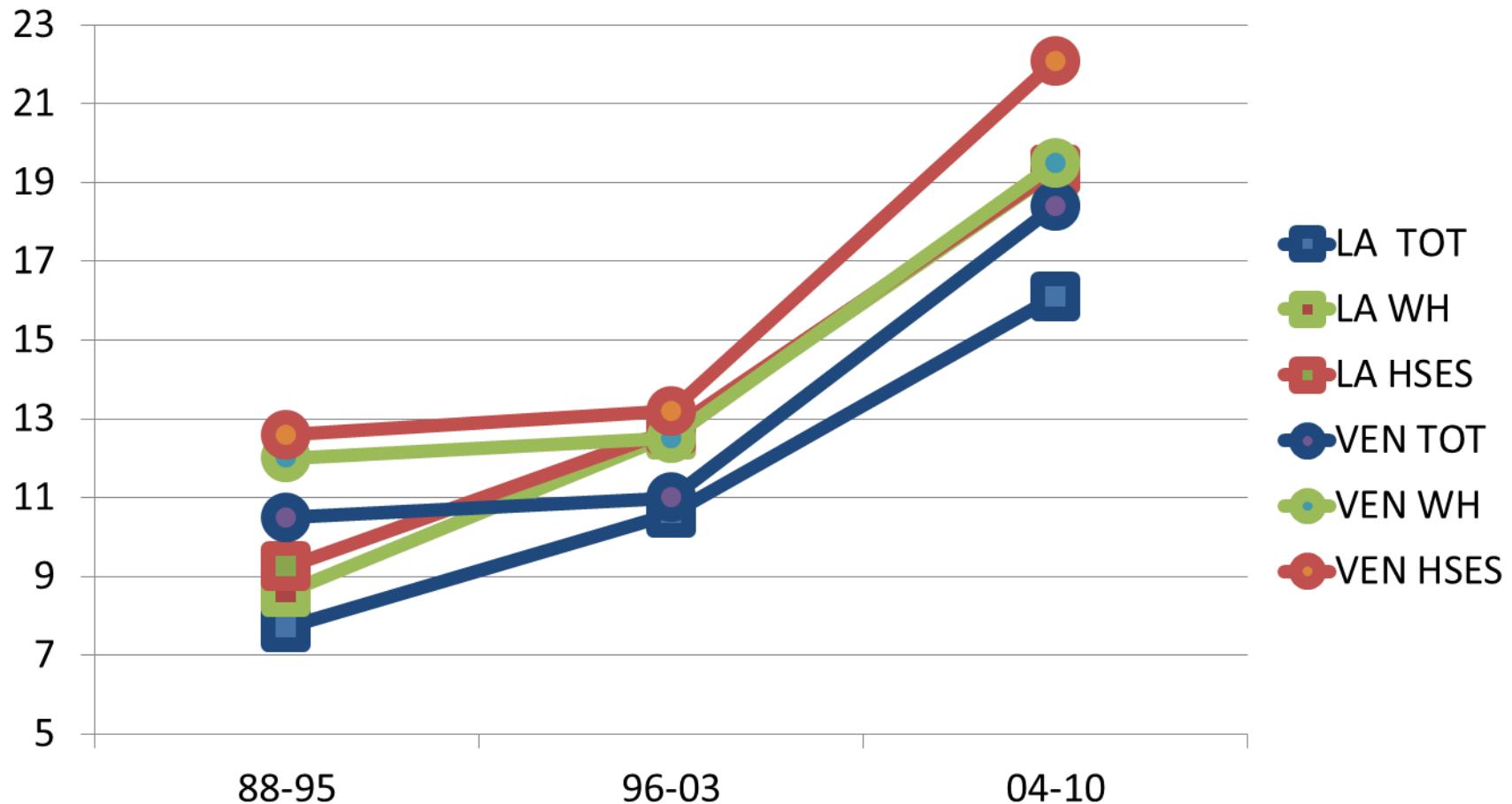
FEMALE BREAST

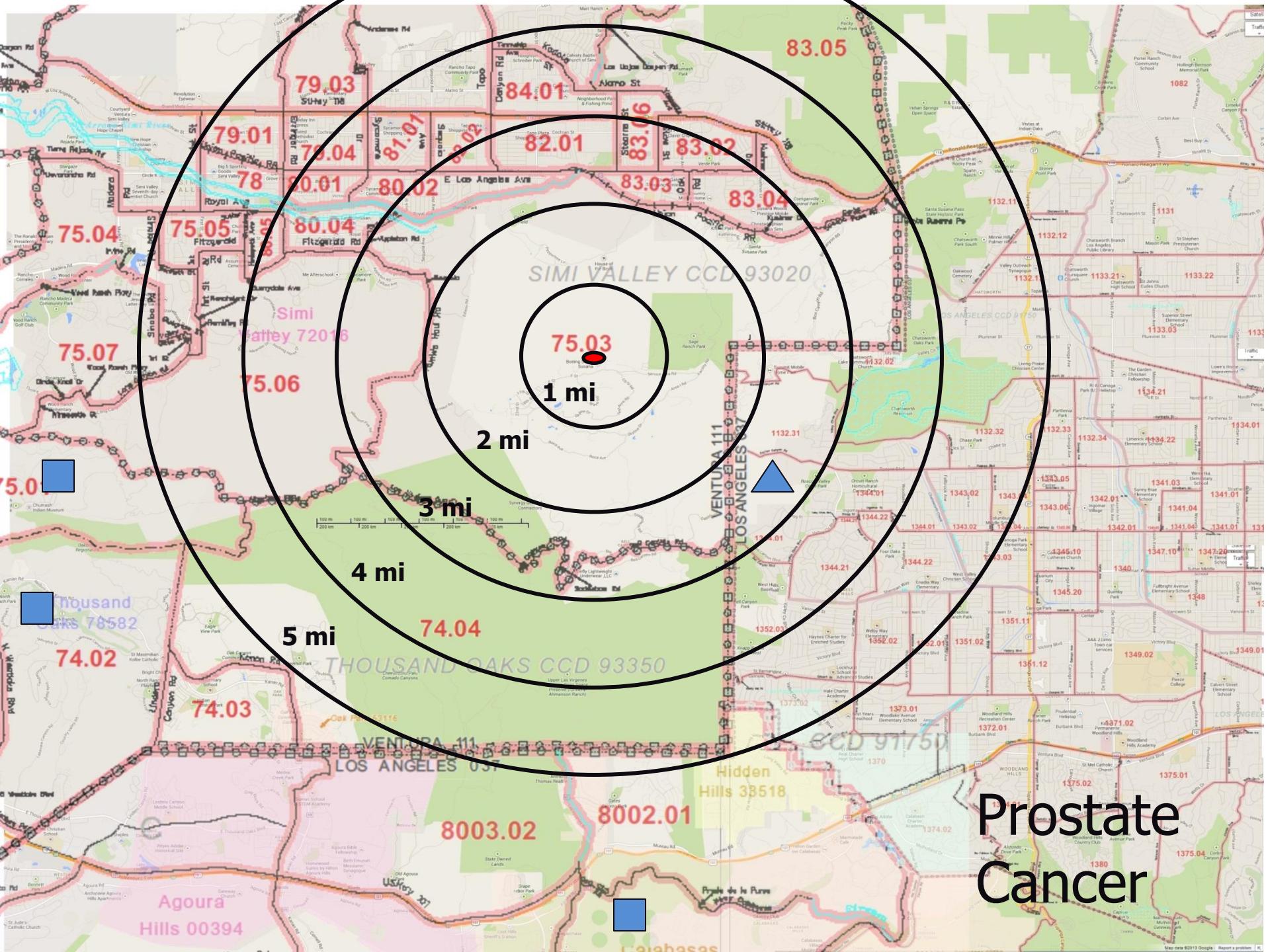




Thyroid Cancer

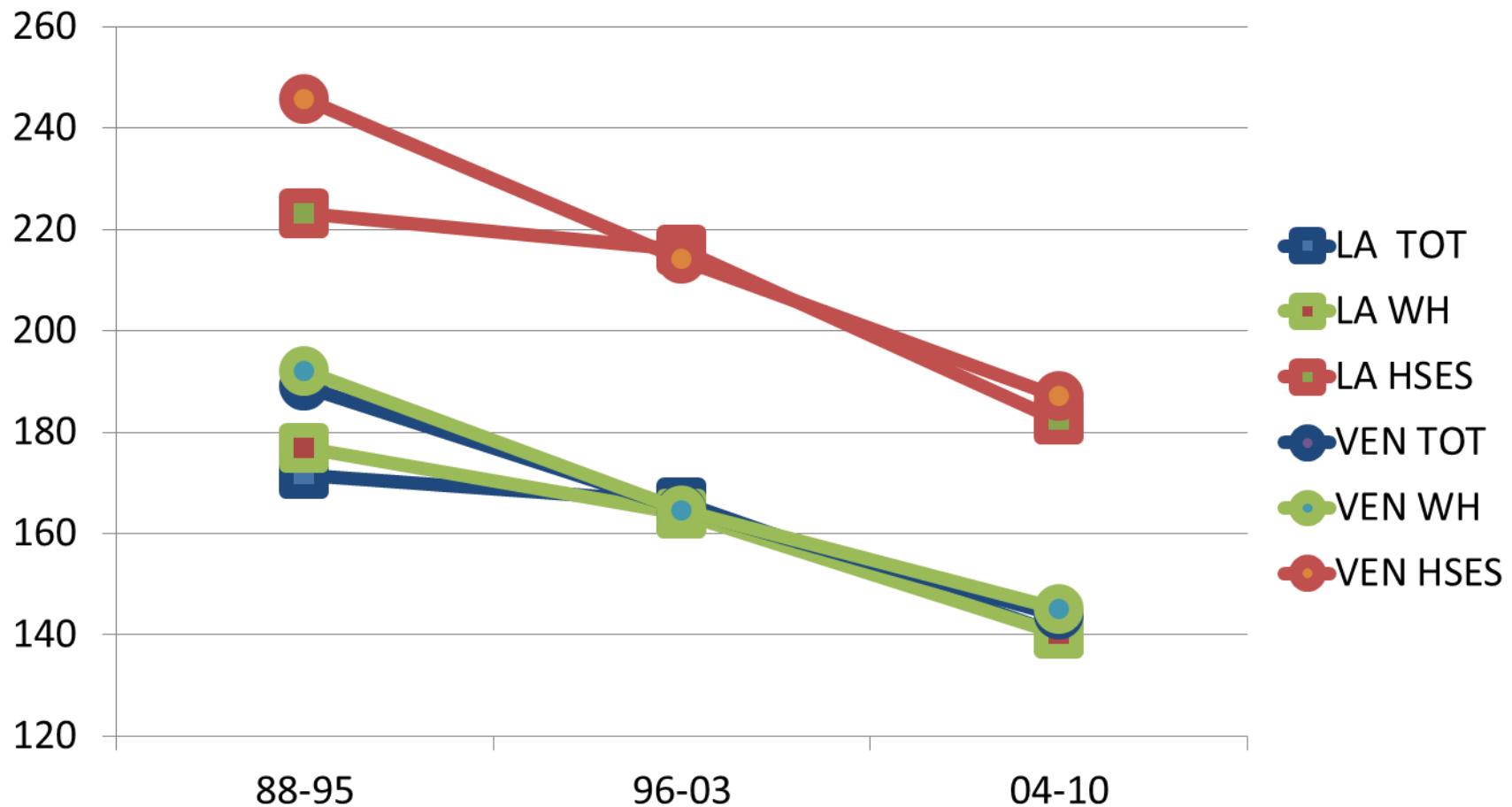
FEMALE THYROID

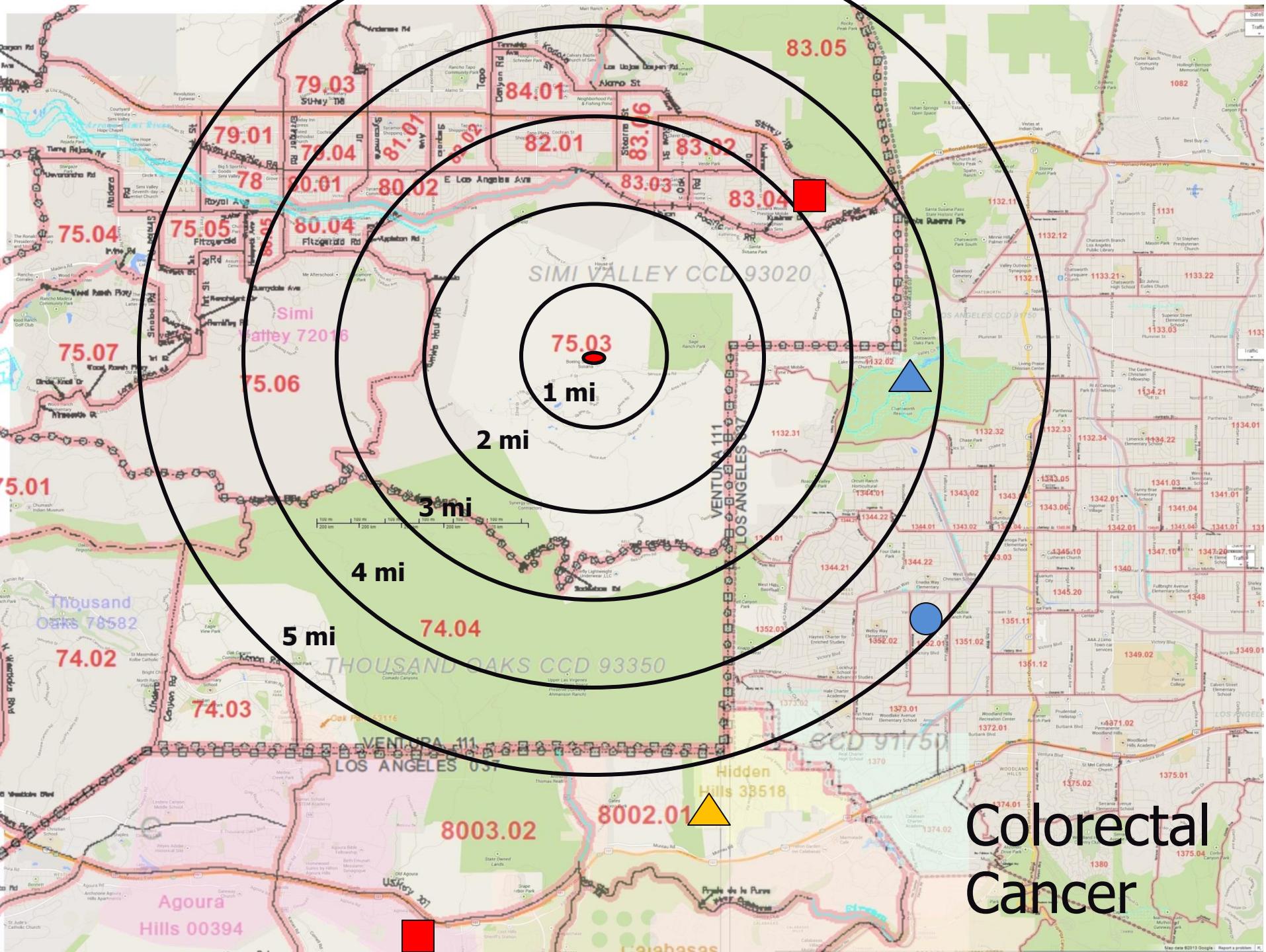




Prostate Cancer

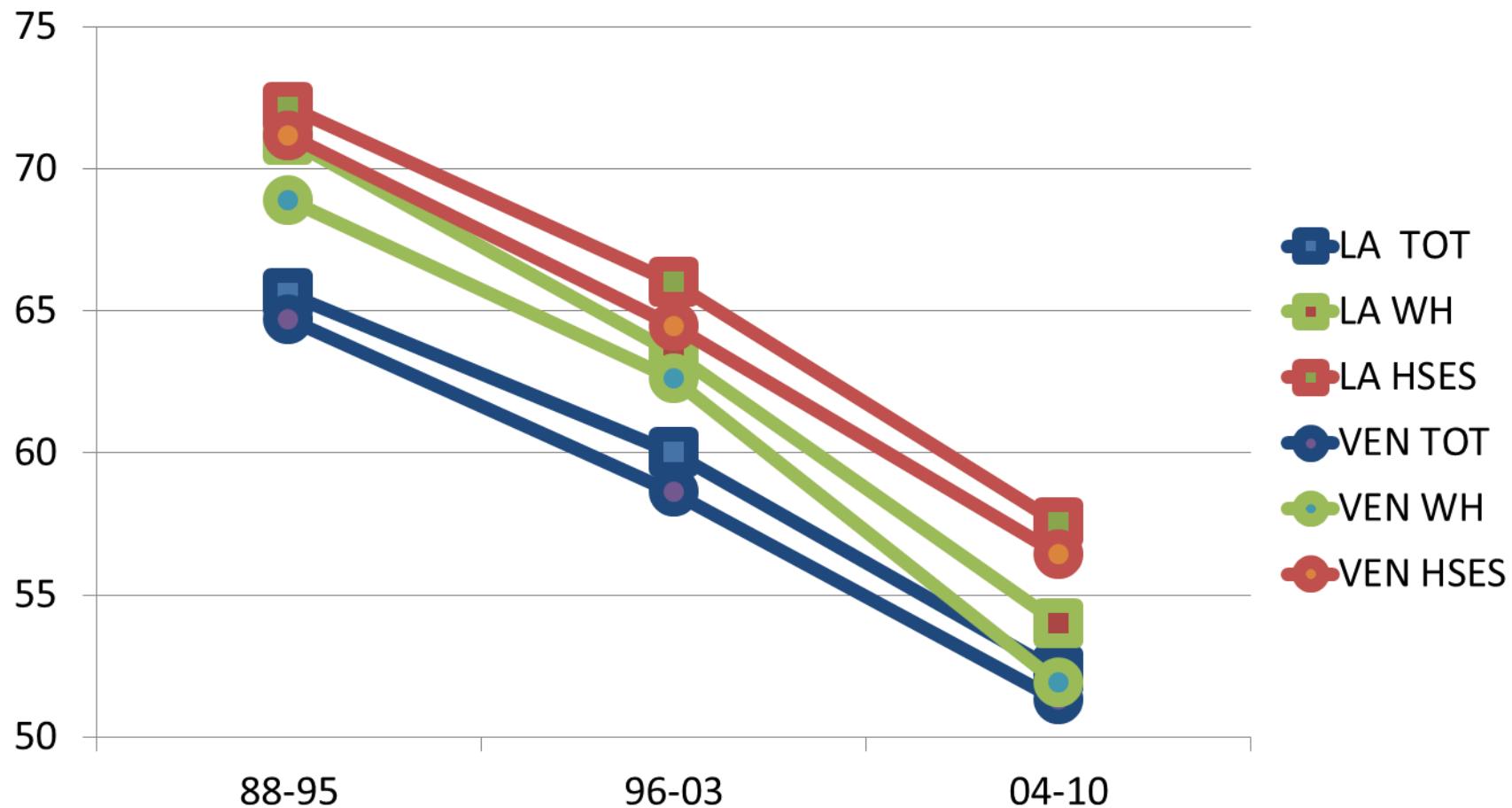
MALE PROSTATE



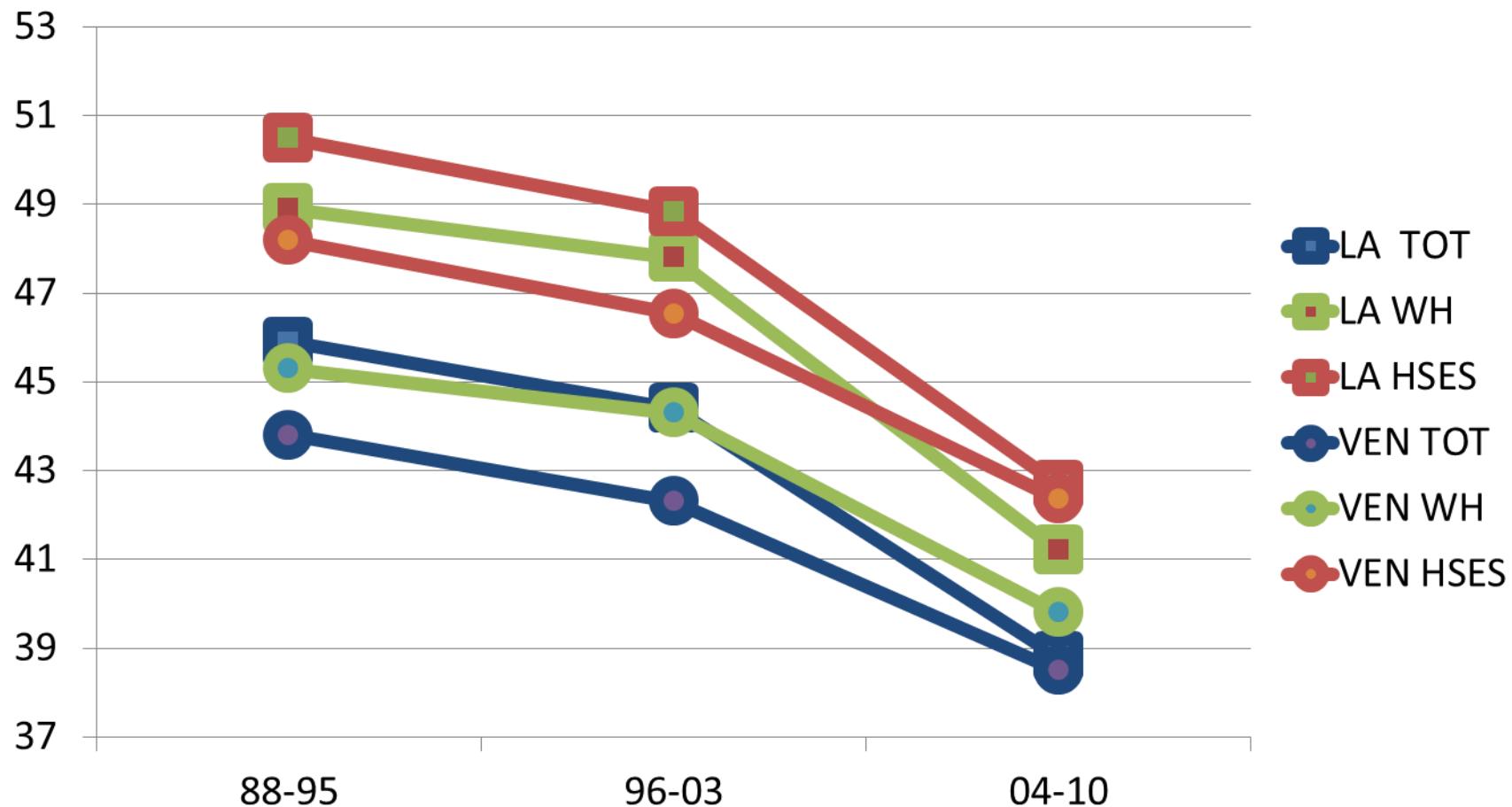


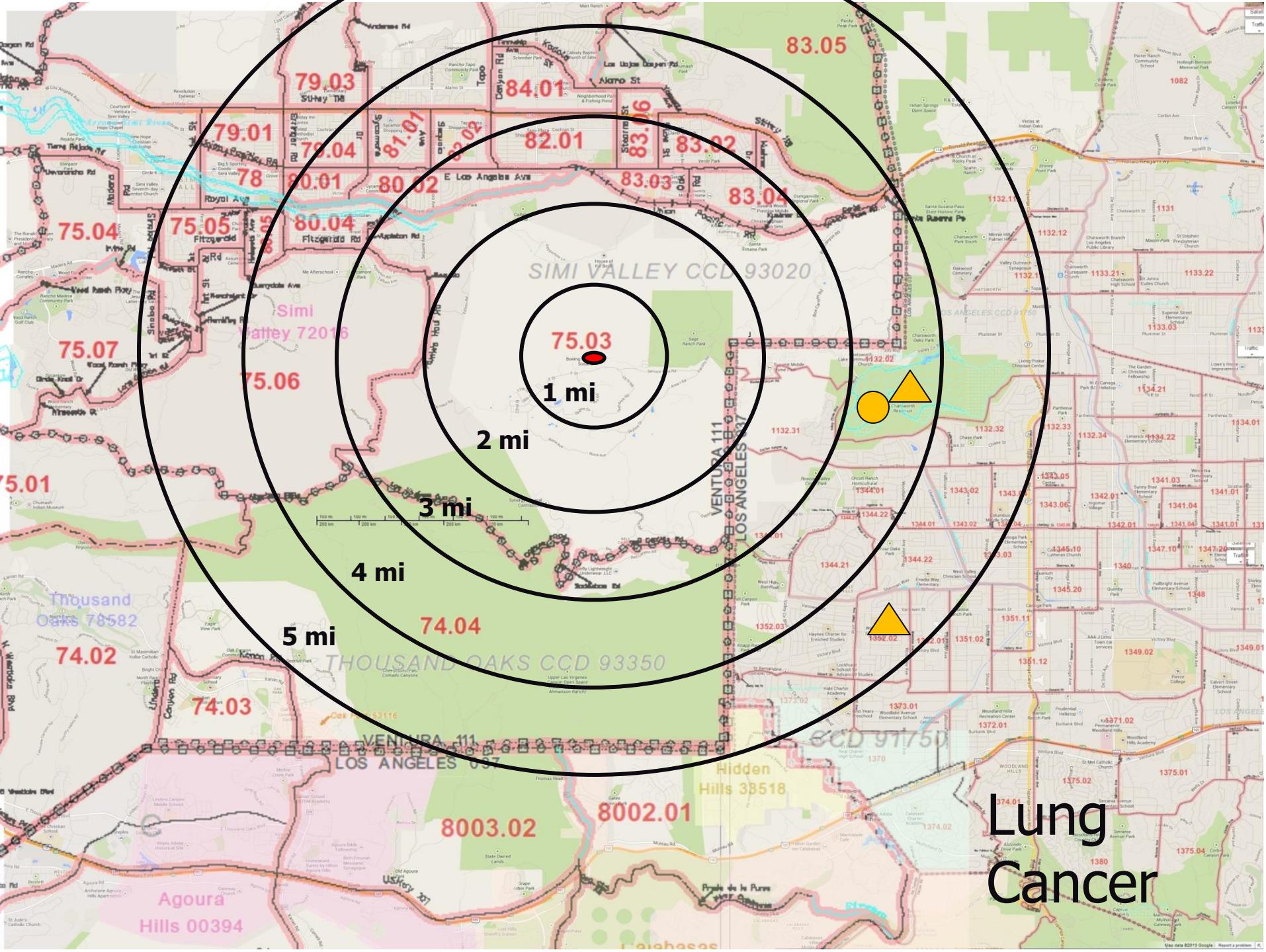
Colorectal Cancer

MALE COLORECTAL



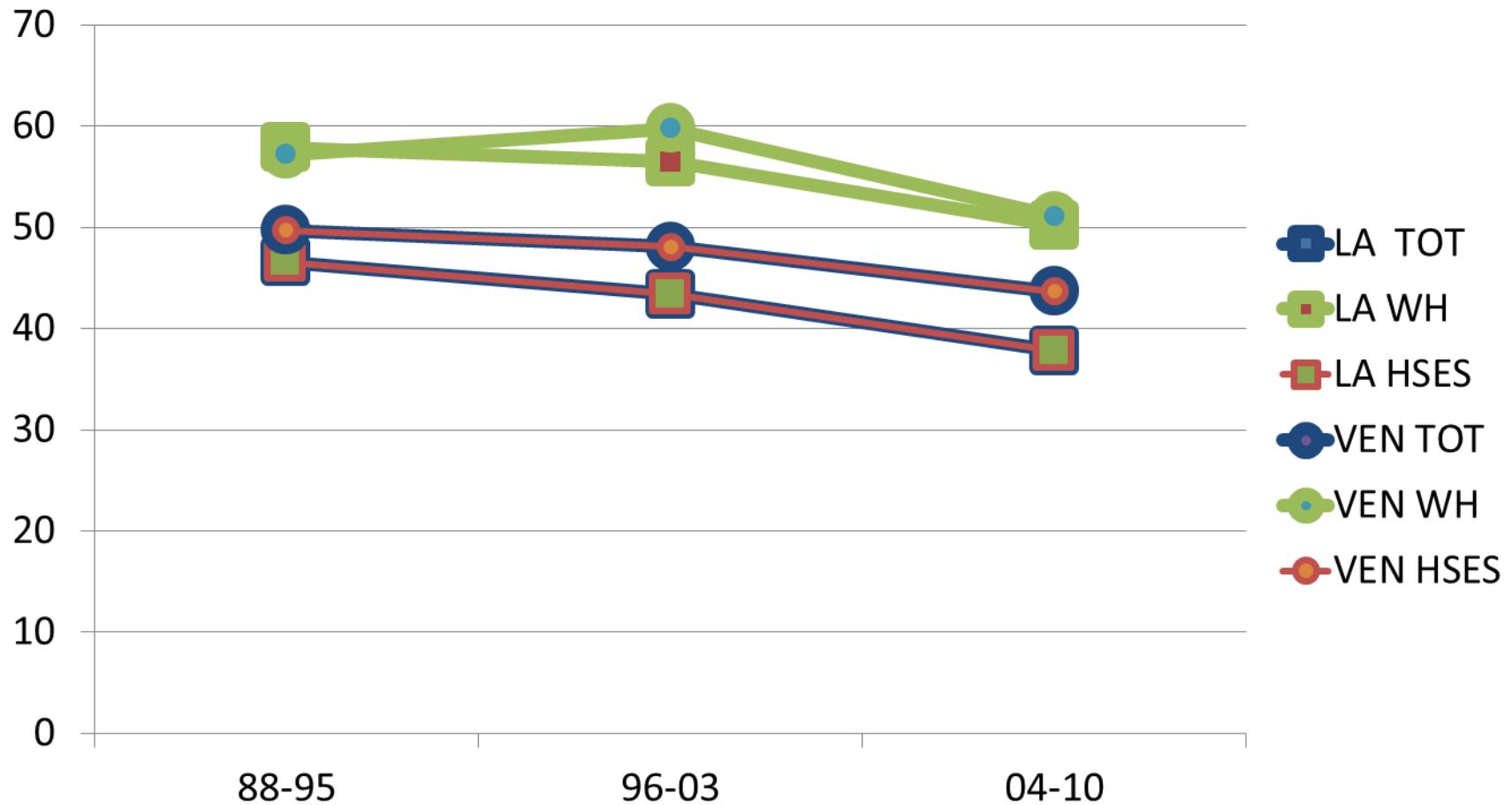
FEMALE COLORECTAL





Lung Cancer

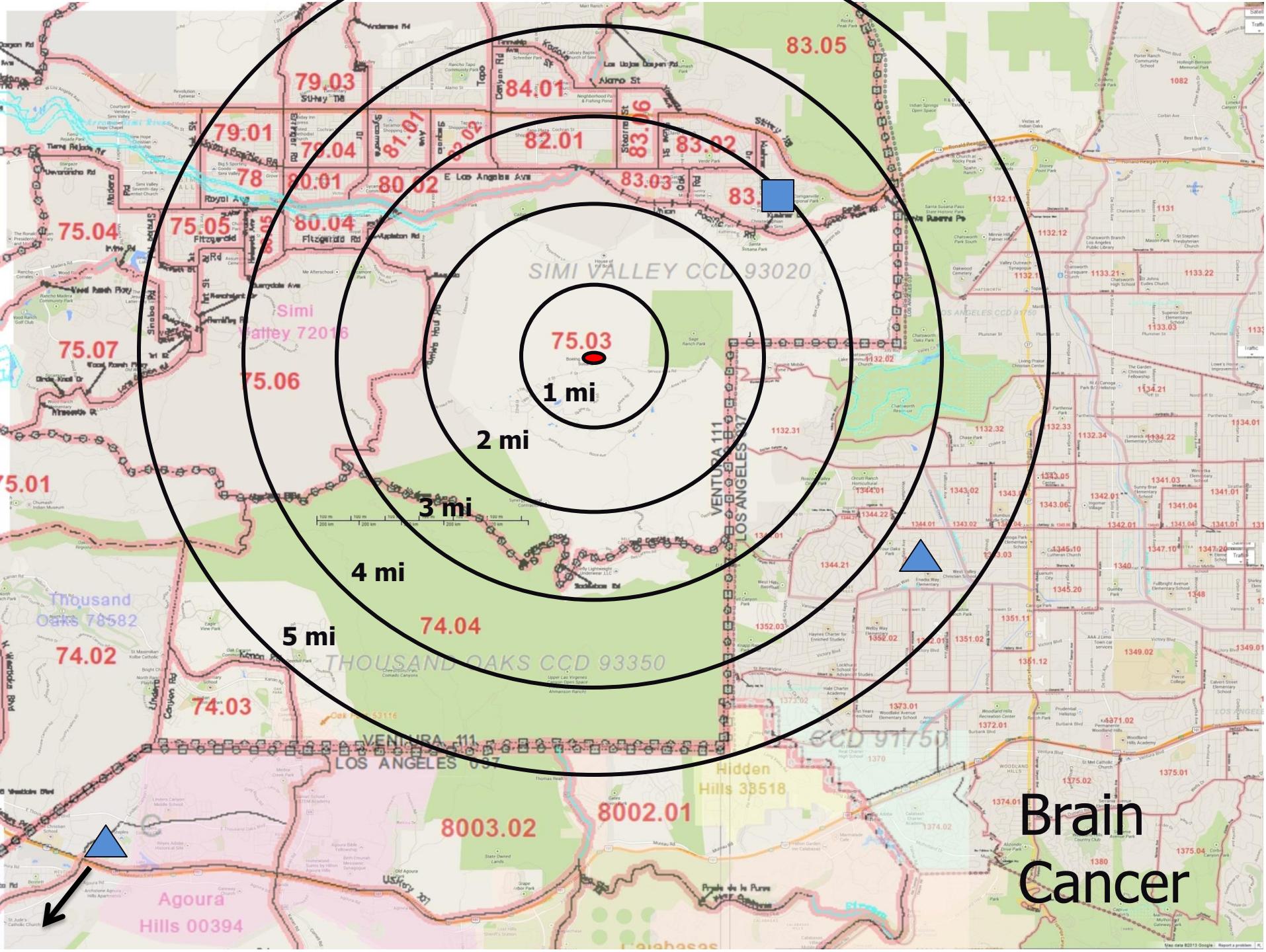
FEMALE LUNG



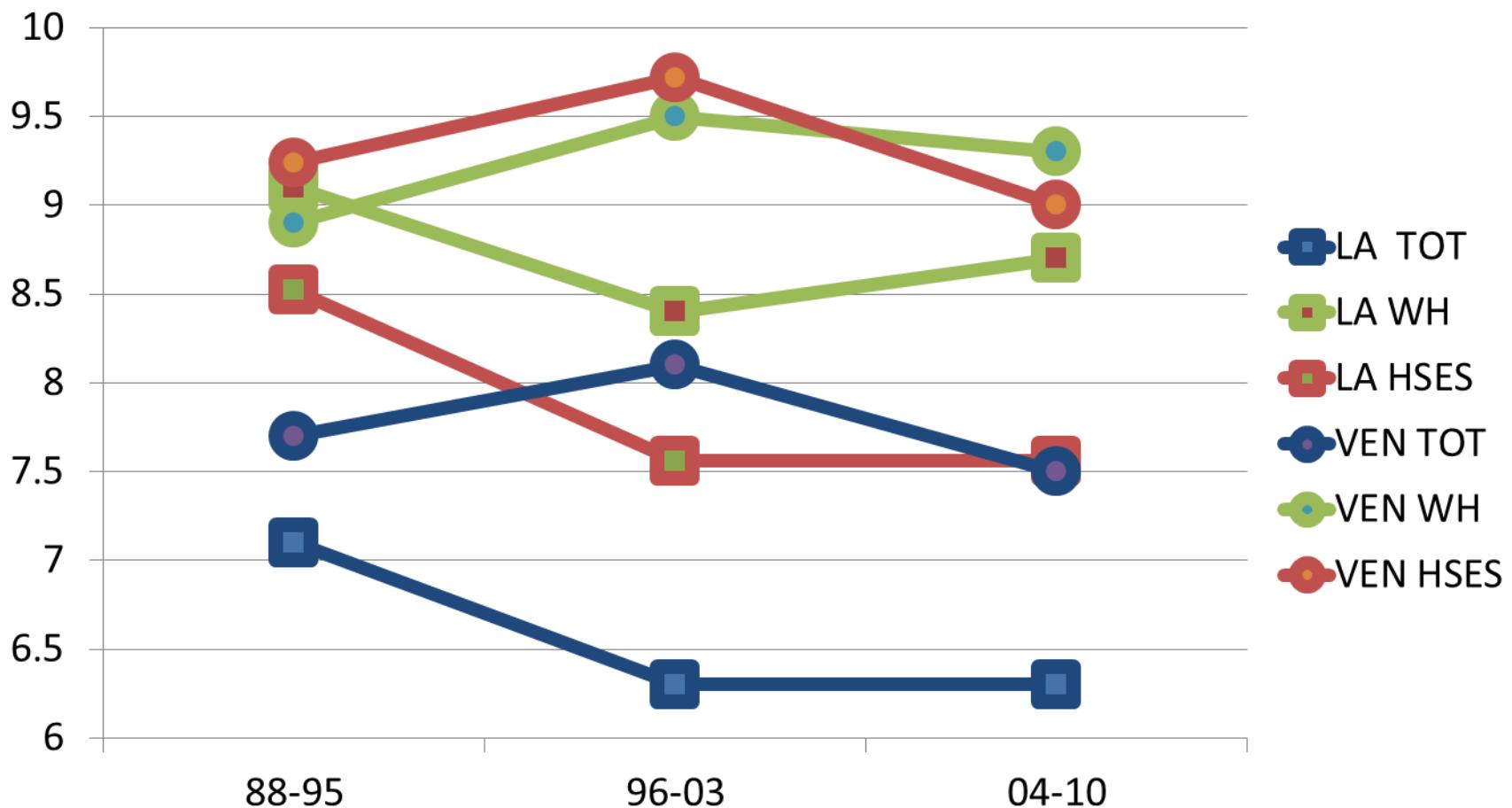
Likely effects of Lifestyle

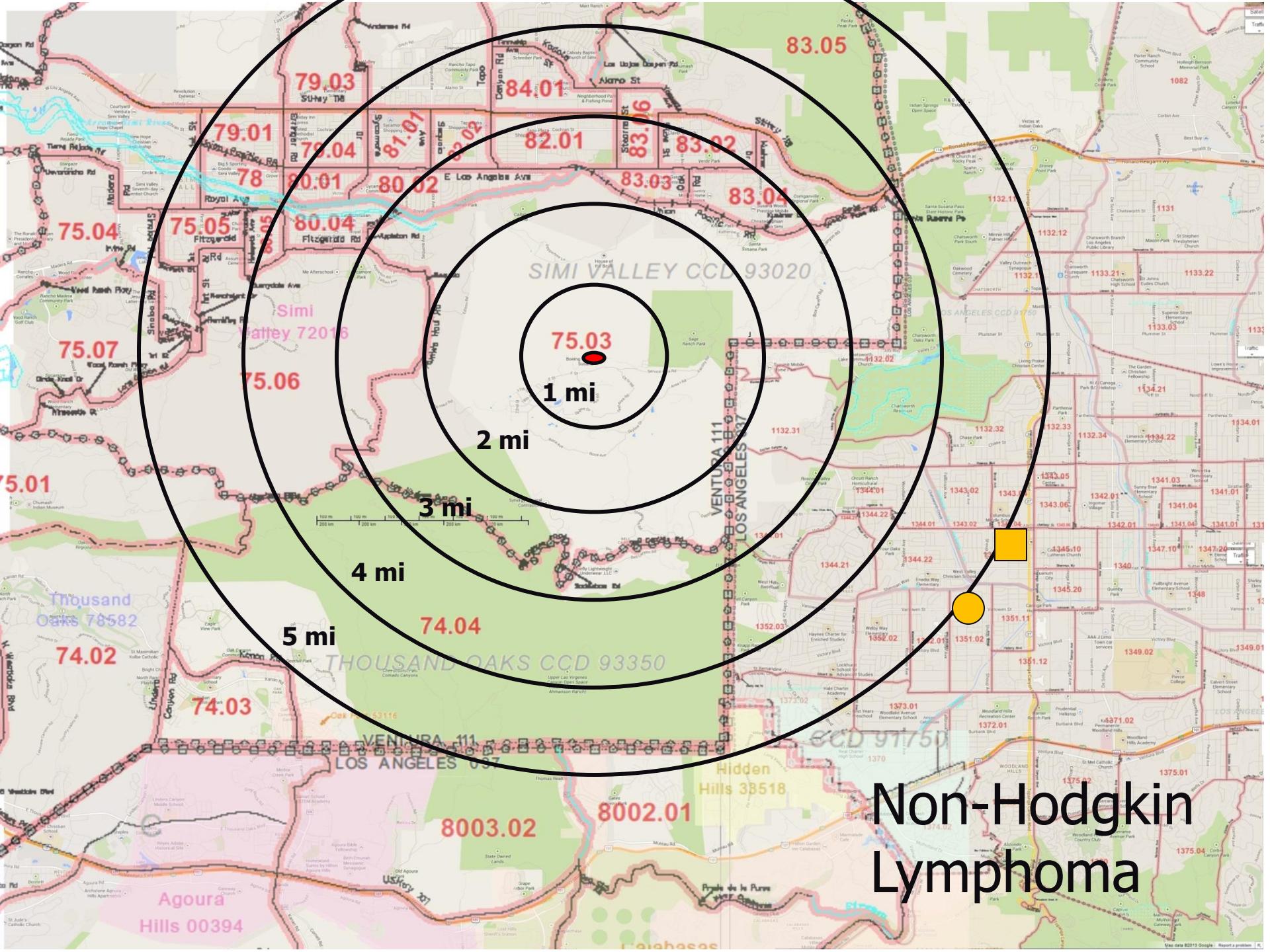
Some clustering of risk is expected

- Breast and Malignant Melanoma
 - Known strong risk of race and high income/education
- Prostate and Thyroid cancers
 - Known to often not progress; commonly found by asymptomatic screening (PSA, ultrasound) with high access to care (high income/education)
- Lung and Colorectal cancers
 - Strongly determined by habitual factors:
 - Smoking for lung, diet/physical inactivity for colorectal



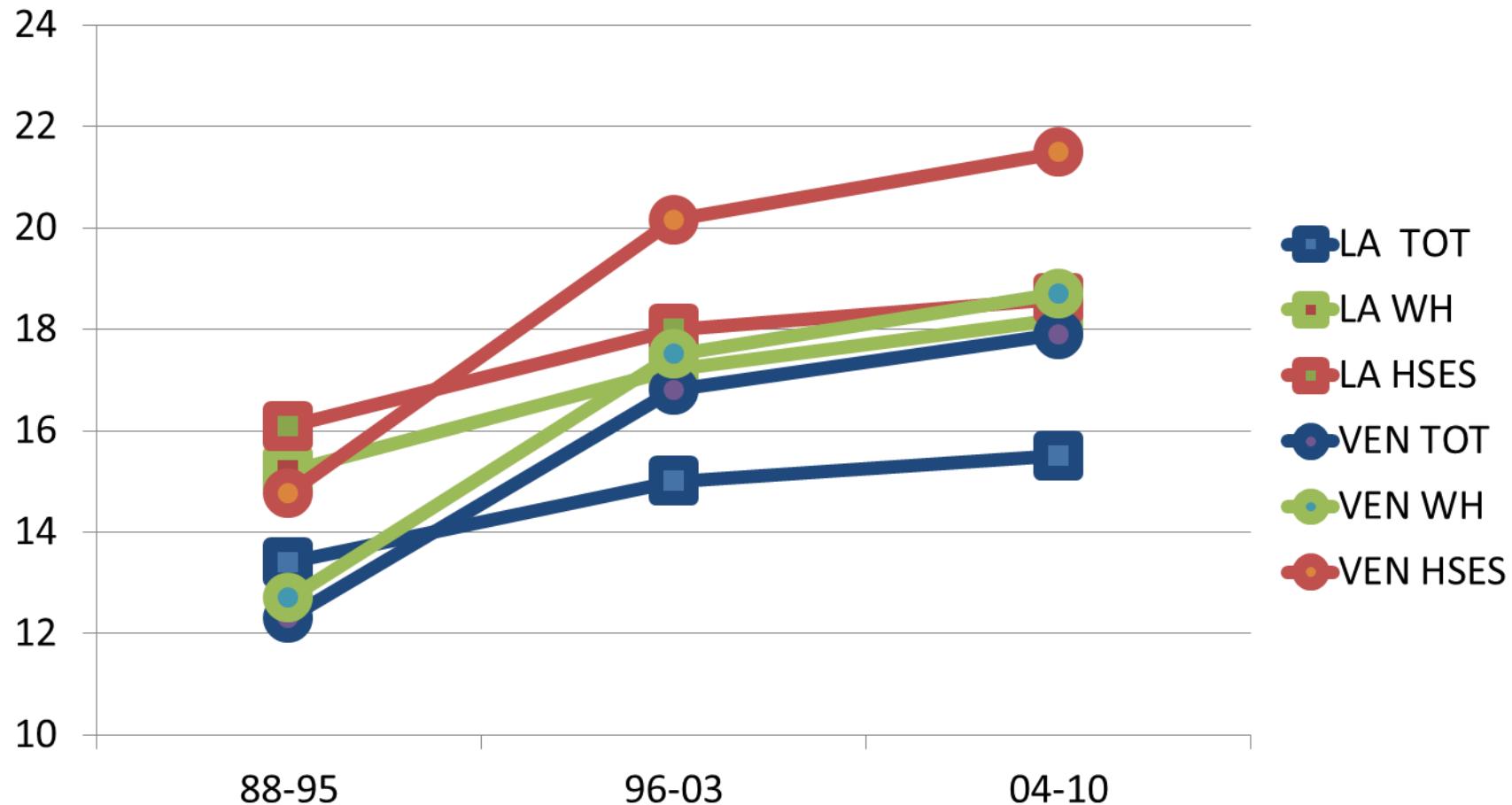
MALE BRAIN

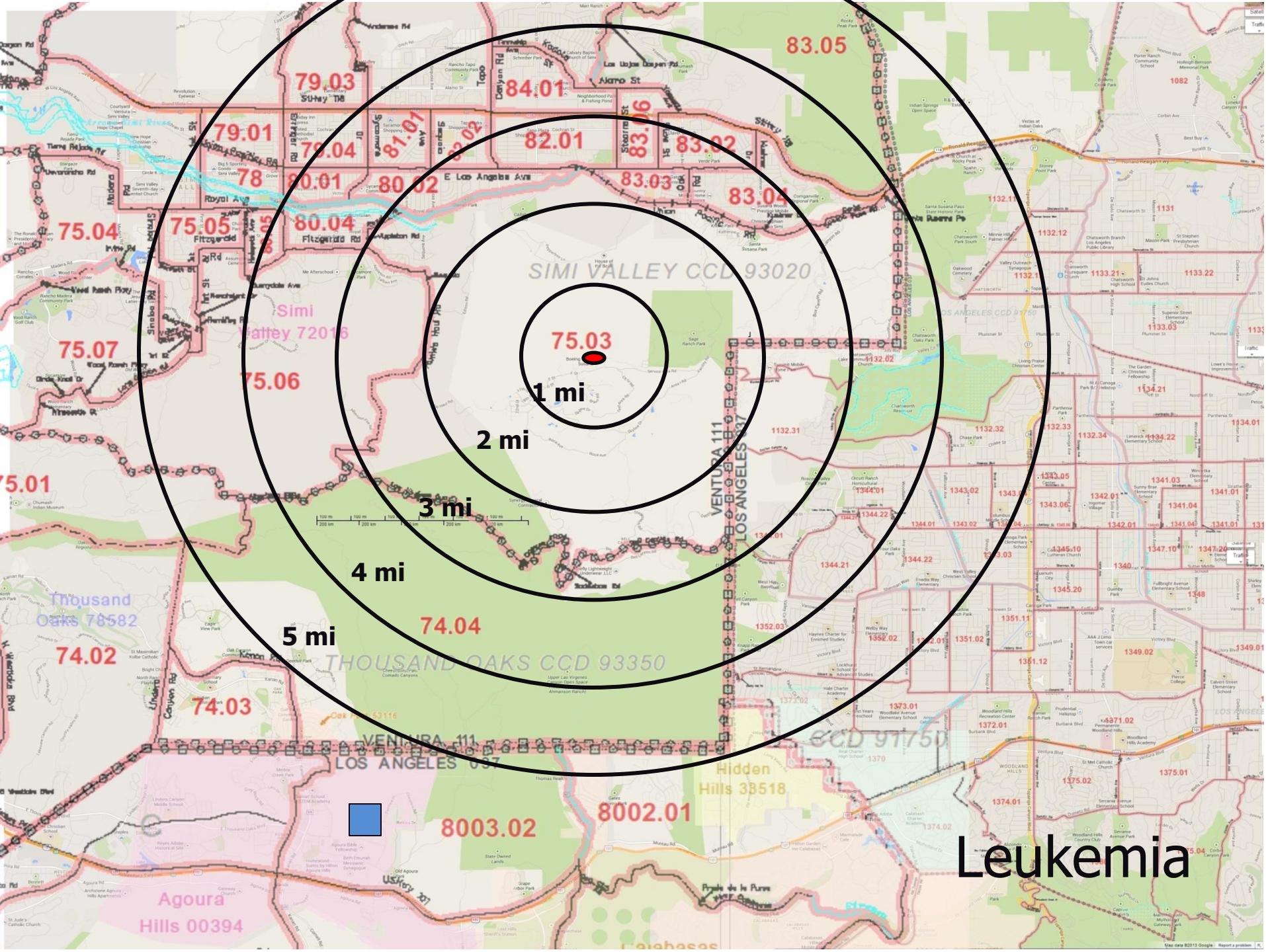




Non-Hodgkin Lymphoma

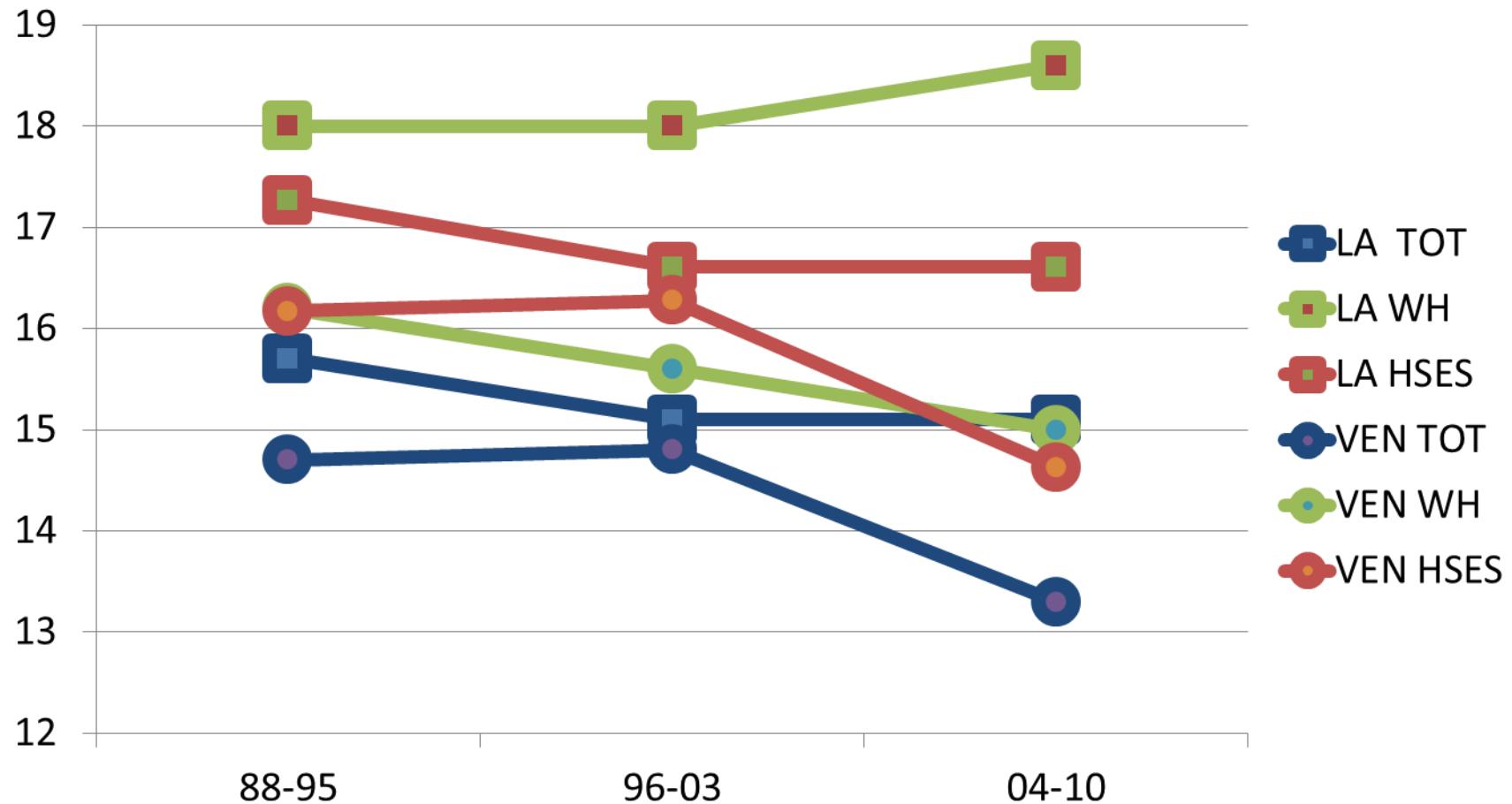
FEMALE NON-HODGKIN'S LYMPHOMA





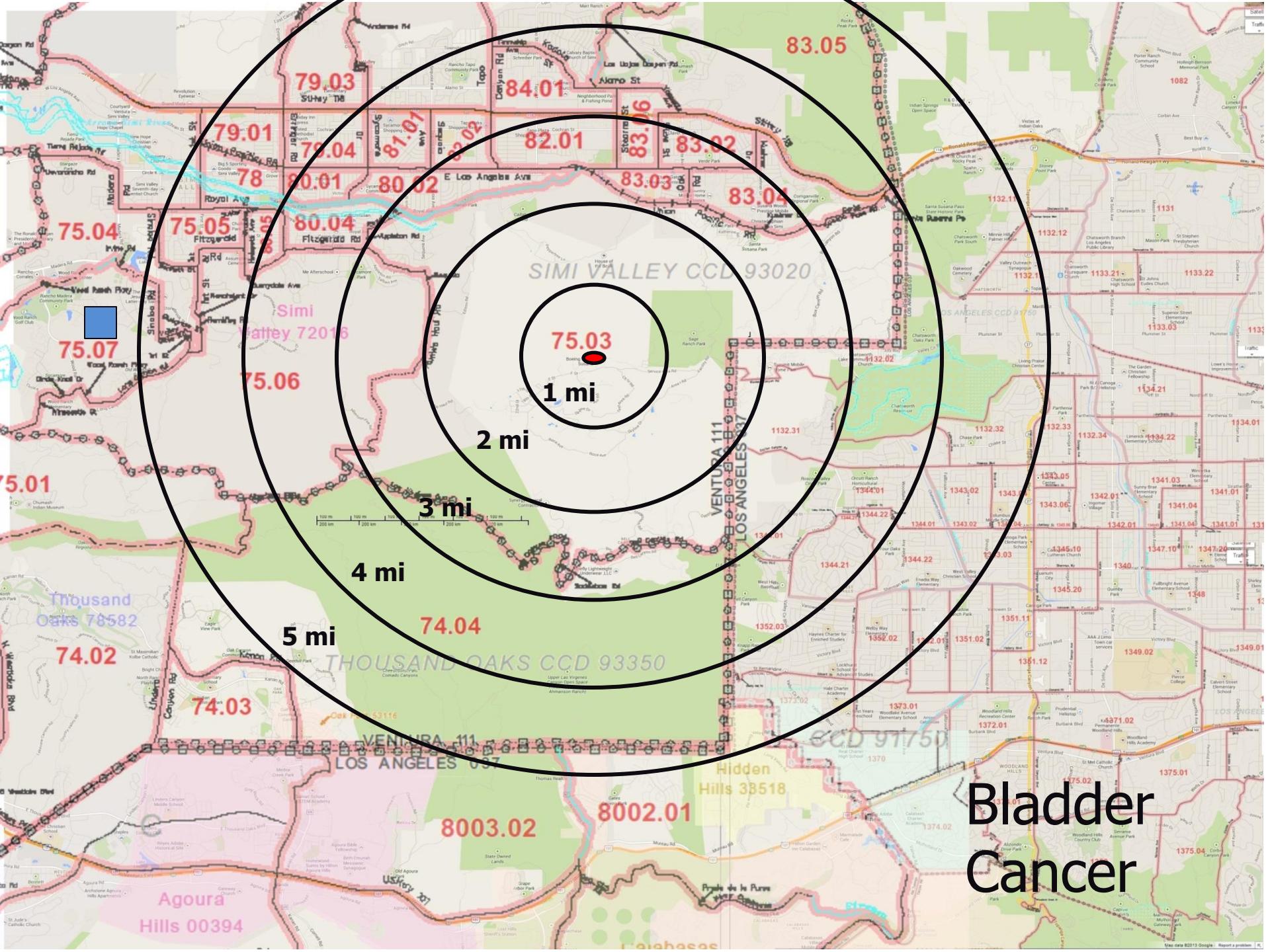
Leukemia

MALE LEUKEMIA



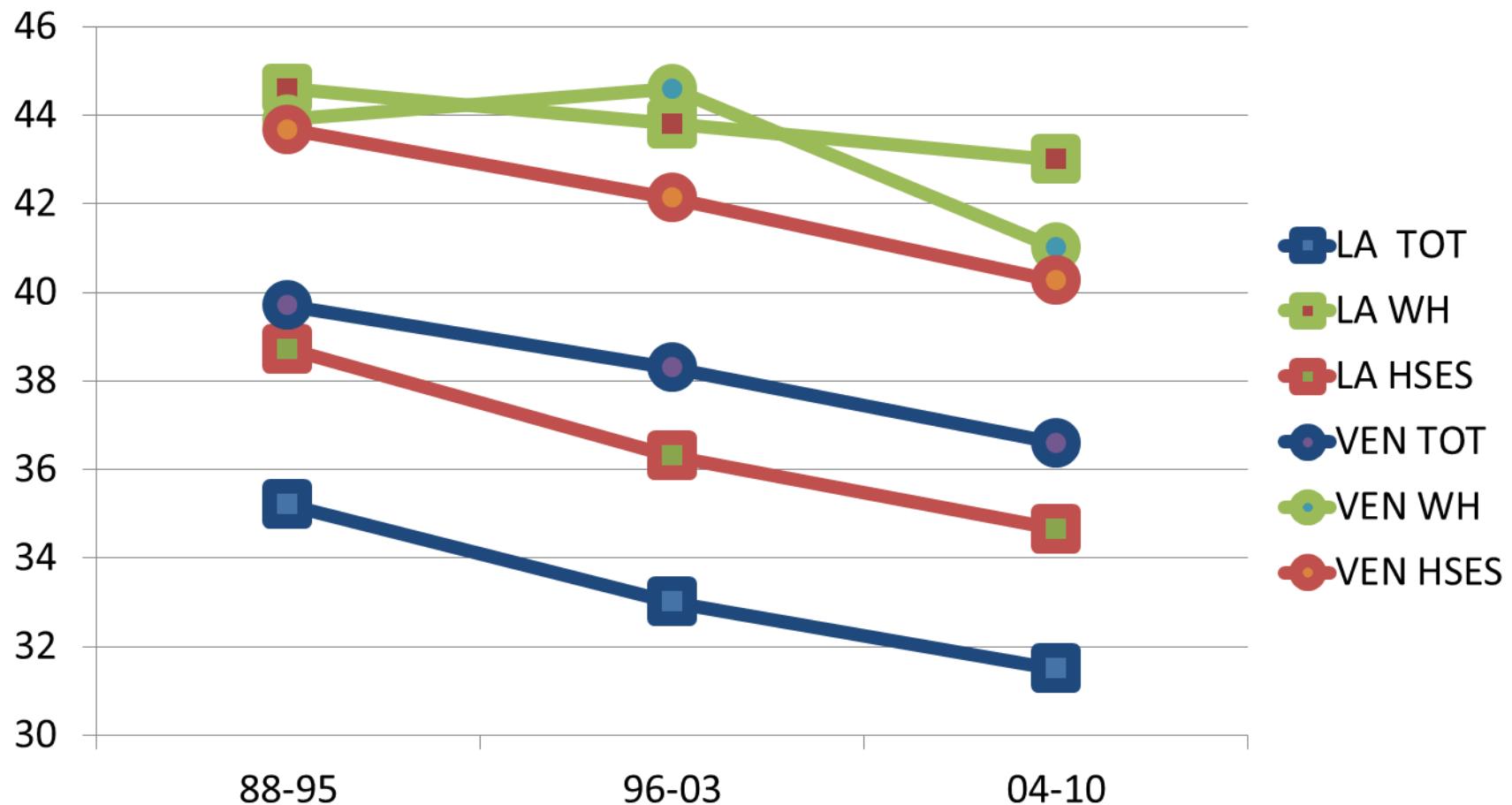
These cancer rubrics oversimplify causal heterogeneity

- Brain: several excess cases are benign, slow-growing tumors with different causes
- Non-Hodgkin lymphoma excess includes at least five different malignancies known to have different causes
- Leukemia excess also is made up of three common and several uncommon varieties
- In each of these, the “high-risk” tracts identified were no more numerous than was expected by chance, and included cases of diverse , most having no known environmental causation



Bladder Cancer

MALE BLADDER



Excess of bladder cancer in one tract in 2004-2010

- Extreme finding: RR >4
- Case tumors had the same common histology
- Most residences scattered, but several are within one mile
- The most prevalent cause of bladder cancer is smoking
- Environmental causes are industrial, waterborne arsenic
- Diagnoses were not clustered in time
- The tract is more than 5 miles to the west of SSFL
- Residential community: no known exposure, specifically no high arsenic in tap water, no local industry, no increase in kidney cancer (another arsenic outcome)
- 66% of the cases were >75 at diagnosis, and all but one of those was over 85.
- Census may have undercounted seniors

Neoplasm	“Significant” tract-periods	Observed/Expected number per tract	Interpretation	Estimated number of CA tracts with that many or more cases
NHL	2 (3 exp. by chance)	8/2.5 12/5.3	No clustering of high-risk tracts No evidence of proximity to SSFL Mixture of cell types, no trend	50-100
Brain	3 (3 exp. by chance)	6/0.9 8/2.3 11/3.5	No clustering of high-risk tracts No consistent proximity to SSFL Mixture of cell types, no trend	10-50
Leukemia	1 (3 exp. by chance)	7/1.3	No clustering of high risk tracts No evidence of proximity to SSFL Mixture of cell types, no trend	10
Bladder	1 (3 exp. by chance)	11/2.5	No clustering of high risk tracts No evidence of proximity to SSFL No evidence of carcinogens Preponderance of elderly cases ? Smoking, census error	1-2

Conclusion

- It is not possible to completely rule out any offsite carcinogenic effects from SSFL
- No evidence of measureable offsite cancer causation occurring as a result of emissions from the SSFL was found.
- Further, no evidence of any cancer causation by any environmental factor was found.