

Tobacco Use and Cancer Outcomes

Reducing Tobacco-Related Cancer Incidence and Mortality
A National Cancer Policy Forum Workshop
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Cigarette Smoke

- Largest single contributor to cancer risk
 - Shifting views on largest contribution to preventable health risks as compared with obesity
- Over 7000 constituents in cigarette smoke
 - 60+ known carcinogens
 - Aldehydes
 - Benzene
 - Metals (cadmium, nickel, polonium)
 - Nicotine
 - Nitrosamines
 - Polyaromatic hydrocarbons
- Large number of additives
 - Enhance absorption
 - Increase flavor
 - Increase addiction

Additives to Cigarettes (~600)

Here are the first 65 (alphabetical order)

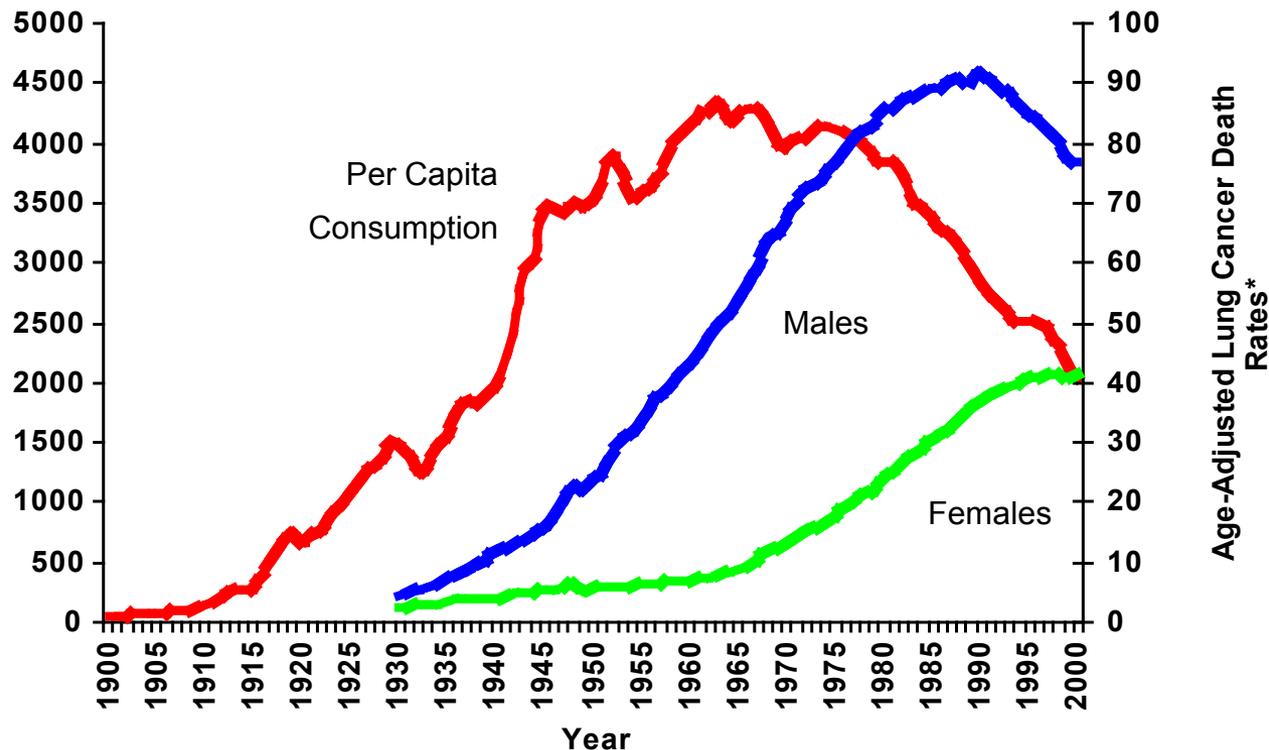
Acetanisole	Ammonium Phosphate Dibasic	1-Asparagine Monohydrate
Acetic Acid	Ammonium Sulfide	1-Aspartic Acid
Acetoin	Amyl Alcohol	Balsam Peru and Oil
Acetophenone	Amyl Butyrate	Basil Oil
6-Acetoxydihydrotheaspirane	Amyl Formate	Bay Leaf, Oil and Sweet Oil
2-Acetyl-3- Ethylpyrazine	Amyl Octanoate	Beeswax White
2-Acetyl-5-Methylfuran	alpha-Amylcinnamaldehyde	Beet Juice Concentrate
Acetylpyrazine	Amyris Oil	Benzaldehyde
2-Acetylpyridine	trans-Anethole	Benzaldehyde Glyceryl Acetal
3-Acetylpyridine	Angelica Root Extract, Oil and Seed Oil	Benzoic Acid, Benzoin
2-Acetylthiazole	Anise	Benzoin Resin
Aconitic Acid	Anise Star, Extract and Oils	Benzophenone
dl-Alanine	Anisyl Acetate	Benzyl Alcohol
Alfalfa Extract	Anisyl Alcohol	Benzyl Benzoate
Allspice Extract,Oleoresin, and Oil	Anisyl Formate	Benzyl Butyrate
Allyl Hexanoate	Anisyl Phenylacetate	Benzyl Cinnamate
Allyl Ionone	Apple Juice Concentrate, Extract, and Skins	Benzyl Propionate
Almond Bitter Oil	Apricot Extract and Juice Concentrate	Benzyl Salicylate
Ambergris Tincture	1-Arginine	Bergamot Oil
Ammonia	Asafetida Fluid Extract And Oil	Bisabolene
Ammonium Bicarbonate	Ascorbic Acid	Black Currant Buds Absolute
Ammonium Hydroxide		Borneol

Additives to Cigarettes (~600)

Acetanisole, Acetic Acid, Acetoin, Acetophenone, 6-Acetoxydihydrotheaspirane, 2-Acetyl-3-Ethylpyrazine, 2-Acetyl-5-Methylfuran, Acetylpyrazine, 2-Acetylpyridine, 3-Acetylpyridine, 2-Acetylthiazole, Aconitic Acid, dl-Alanine, Alfalfa Extract, Allspice Extract, Oleoresin, and Oil, Allyl Hexanoate, Allyl Ionone, Almond Bitter Oil, Ambergis Tincture, Ammonia, Ammonium Bicarbonate, Ammonium Hydroxide, Ammonium Phosphate Dibasic, Ammonium Sulfide, Amyl Alcohol, Amyl Butyrate, Amyl Formate, Amyl Octanoate, alpha-Amylcinnamaldehyde, Amyris Oil, trans-Anethole, Angelica Root Extract, Oil and Seed Oil, Anise, Anise Star, Extract and Oils, Anisyl Acetate, Anisyl Alcohol, Anisyl Formate, Anisyl Phenylacetate, Apple Juice Concentrate, Extract, and Skins, Apricot Extract and Juice Concentrate, 1-Arginine, Asafetida Fluid Extract And Oil, Ascorbic Acid, 1-Asparagine Monohydrate, 1-Aspartic Acid, Balsam Peru and Oil, Basil Oil, Bay Leaf, Oil and Sweet Oil, Beeswax White, Beet Juice Concentrate, Benzaldehyde, Benzaldehyde Glyceryl Acetal, Benzoic Acid, Benzoin, Benzoin Resin, Benzophenone, Benzyl Alcohol, Benzyl Benzoate, Benzyl Butyrate, Benzyl Cinnamate, Benzyl Propionate, Benzyl Salicylate, Bergamot Oil, Bisabolene, Black Currant Buds Absolute, Borneol, Borneyl Acetate, Buchu Leaf Oil, 1,3-Butanediol, 2,3-Butanedione, 1-Butanol, 2-Butanone, 4(2-Butenylidene)-3,5,5-Trimethyl-2-Cyclohexen-1-One, Butter, Butter Esters, and Butter Oil, Butyl Acetate, Butyl Butyrate, Butyl Butyryl Lactate, Butyl Isovalerate, Butyl Phenylacetate, Butyl Undecylenate, 3-Butyridenephthalide, Butyric Acid, Cadinene, Caffeine, Calcium Carbonate, Camphene, Cananga Oil, Capsicum Oleoresin, Caramel Color, Caraway Oil, Carbon Dioxide, Cardamom Oleoresin, Extract, Seed Oil, and Powder, Carob Bean and Extract, beta-Carotene, Carrot Oil, Carvacrol, 4-Carvomenthenol, 1-Carvone, beta-Caryophyllene, beta-Caryophyllene Oxide, Cascarella Oil and Bark Extract, Cassia Bark Oil, Cassie Absolute and Oil, Castoreum Extract, Tincture and Absolute, Cedar Leaf Oil, Cedarwood Oil Terpenes and Virginiana, Cedrol, Celery Seed Extract, Solid, Oil, And Oleoresin, Cellulose Fiber, Chamomile Flower Oil And Extract, Chicory Extract, Chocolate, Cinnamaldehyde, Cinnamic Acid, Cinnamon Leaf Oil, Bark Oil, and Extract, Cinnamyl Acetate, Cinnamyl Alcohol, Cinnamyl Cinnamate, Cinnamyl Isovalerate, Cinnamyl Propionate, Citral, Citric Acid, Citronella Oil, dl-Citronellol, Citronellyl Butyrate, itronellyl Isobutyrate, Civet Absolute, Clary Oil, Clover Tops, Red Solid Extract, Cocoa, Cocoa Shells, Extract, Distillate And Powder, Coconut Oil, Coffee, Cognac White and Green Oil, Copaiba Oil, Coriander, Extract and Oil, Corn Oil, Corn Silk, Costus Root Oil, Cubeb Oil, Cuminaldehyde, para-Cymene, 1-Cysteine, Dandelion Root Solid Extract, Davana Oil, 2-trans, 4-trans-Decadienal, delta-Decalactone, gamma-Decalactone, Decanal, Decanoic Acid, 1-Decanol, 2-Decenal, Dehydromenthofurrolactone, Diethyl Malonate, Diethyl Sebacate, 2,3-Diethylpyrazine, Dihydro Anethole, 5,7-Dihydro-2-Methylthieno(3,4-D) Pyrimidine, Dill Seed Oil and Extract, meta-Dimethoxybenzene, para-Dimethoxybenzene, 2,6-Dimethoxyphenol, Dimethyl Succinate, 3,4-Dimethyl-1,2-Cyclopentanedione, 3,5-Dimethyl-1,2-Cyclopentanedione, 3,7-Dimethyl-1,3,6-Octatriene, 4,5-Dimethyl-3-Hydroxy-2,5-Dihydrofuran-2-One, 6,10-Dimethyl-5,9-Undecadien-2-One, 3,7-Dimethyl-6-Octenoic Acid, 2,4-Dimethylacetophenone, alpha,para-Dimethylbenzyl Alcohol, alpha,alpha-Dimethylphenethyl Acetate, alpha,alpha-Dimethylphenethyl Butyrate, 2,3-Dimethylpyrazine, 2,5-Dimethylpyrazine, 2,6-Dimethylpyrazine, Dimethyltetrahydrobenzofuranone, delta-Dodecalactone, gamma-Dodecalactone, para-Ethoxybenzaldehyde, Ethyl 10-Undecenoate, Ethyl 2-Methylbutyrate, Ethyl Acetate, Ethyl Acetoacetate, Ethyl Alcohol, Ethyl Benzoate, Ethyl Butyrate, Ethyl Cinnamate, Ethyl Decanoate, Ethyl Fenchol, Ethyl Furoate, Ethyl Heptanoate, Ethyl Hexanoate, Ethyl Isovalerate, Ethyl Lactate, Ethyl Laurate, Ethyl Levulinate, Ethyl Maltol, Ethyl Methyl Phenylglycidate, Ethyl Myristate, Ethyl Nonanoate, Ethyl Octadecanoate, Ethyl Octanoate, Ethyl Oleate, Ethyl Palmitate, Ethyl Phenylacetate, Ethyl Propionate, Ethyl Salicylate, Ethyl trans-2-Butenoate, Ethyl Valerate, Ethyl Vanillin, 2-Ethyl (or Methyl)-(3,5 and 6)-Methoxypyrazine, 2-Ethyl-1-Hexanol, 3-Ethyl -2-Hydroxy-2-Cyclopenten-1-One, 2-Ethyl-3, (5 or 6)-Dimethylpyrazine, 5-Ethyl-3-Hydroxy-4-Methyl-2(5H)-Furanone, 2-Ethyl-3-Methylpyrazine, 4-Ethylbenzaldehyde, 4-Ethylguaiaicol, para-Ethylphenol, 3-Ethylpyridine, Eucalyptol, Farnesol, D-Fenchone, Fennel Sweet Oil, Fenugreek Extract, Resin, and Absolute, Fig Juice Concentrate, Food Starch Modified, Furfuryl Mercaptan, 4-(2-Furyl)-3-Buten-2-One, Galbanum Oil, Genet Absolute, Gentian Root Extract, Geraniol, Geranium Rose Oil, Geranyl Acetate, Geranyl Butyrate, Geranyl Formate, Geranyl Isovalerate, Geranyl Phenylacetate, Ginger Oil and Oleoresin, 1-Glutamic Acid, 1-Glutamine, Glycerol, Glycyrrhizin Ammoniated, Grape Juice Concentrate, Guaiaic Wood Oil, Guaiaicol, Guar Gum, 2,4-Heptadienal, gamma-Heptalactone, Heptanoic Acid, 2-Heptanone, 3-Hepten-2-One, 2-Hepten-4-One, 4-Heptenal, trans -2-Heptenal, Heptyl Acetate, omega-6-Hexadecenalactone, gamma-Hexalactone, Hexanal, Hexanoic Acid, 3-Hexen-1-Ol, 3-Hexen-1-Yl Acetate, 2-Hexenal, 3-Hexenoic Acid, trans-2-Hexenoic Acid, cis-3-Hexenyl-Formate, Hexyl 2-Methylbutyrate, Hexyl Acetate, Hexyl Alcohol, Hexyl Phenylacetate, 1-Histidine, Honey, Hops Oil, Hydrolyzed Milk Solids, Hydrolyzed Plant Proteins, 5-Hydroxy-2,4-Decadienoic Acid delta- Lactone, 4-Hydroxy-2,5-Dimethyl-3(2H)-Furanone, 2-Hydroxy-3,5,5-Trimethyl-2-Cyclohexen-1-One, 4-Hydroxy -3-Pentenoic Acid Lactone, 2-Hydroxy-4-Methylbenzaldehyde, 4-Hydroxybutanoic Acid Lactone, Hydroxycitronellal, 6-Hydroxydihydrotheaspirane, 4-(para-Hydroxyphenyl)-2-Butanone, Hyssop Oil, Immortelle Absolute and Extract, alpha-Ionone, beta-Ionone, alpha-Irone, Isoamyl Acetate, Isoamyl Benzoate, Isoamyl Butyrate, Isoamyl Cinnamate, Isoamyl Formate, Isoamyl Hexanoate, Isoamyl Isovalerate, Isoamyl Octanoate, Isoamyl Phenylacetate, Isobornyl Acetate, Isobutyl Acetate, Isobutyl Alcohol, Isobutyl Cinnamate, Isobutyl Phenylacetate, Isobutyl Salicylate, 2-Isobutyl-3-Methoxypyrazine, alpha-Isobutylphenethyl Alcohol, Isobutyraldehyde, Isobutyric Acid, d,l-Isoleucine, alpha-Isomethylionone, 2-Isopropylphenol, Isovaleric Acid, Jasmine Absolute, Concrete and Oil, Kola Nut Extract, Labdanum Absolute and Oleoresin, Lactic Acid, Lauric Acid, Lauric Aldehyde, Lavandin Oil, Lavender Oil, Lemon Oil and Extract, Lemongrass Oil, 1-Leucine, Levulinic Acid, Licorice Root, Fluid, Extract and Powder, Lime Oil, Linalool, Linalool Oxide, Linalyl Acetate, Linden Flowers, Lovage Oil And Extract, 1-Lysine, Mace Powder, Extract and Oil, Magnesium Carbonate, Malic Acid, Malt and Malt Extract, Maltodextrin, Maltol, Maltyl Isobutyrate, Mandarin Oil, Maple Syrup and Concentrate, Mate Leaf, Absolute and Oil, para-Mentha-8-Thiol-3-One, Menthol, Menthone, Menthyl Acetate, dl-Methionine, Methoprene, 2-Methoxy-4-Methylphenol, 2-Methoxy-4-Vinylphenol, para-Methoxybenzaldehyde, 1-(para-Methoxyphenyl)-1-Penten-3-One, 4-(para-Methoxyphenyl)-2-Butanone, 1-(para-Methoxyphenyl)-2-Propanone, Methoxypyrazine, Methyl 2-Furoate, Methyl 2-Octynoate, Methyl 2-Pyrrolyl Ketone, Methyl Anisate, Methyl Anthranilate, Methyl Benzoate, Methyl Cinnamate, Methyl Dihydrojasmonate, Methyl Ester of Rosin, Partially Hydrogenated, Methyl Isovalerate, Methyl Linoleate (48%), Methyl Linolenate (52%) Mixture, Methyl Naphthyl Ketone, Methyl Nicotinate, Methyl Phenylacetate, Methyl Salicylate, Methyl Sulfide, 3-Methyl-1-Cyclopentadecanone, 4-Methyl-1-Phenyl-2-Pentanone, 5-Methyl-2-Phenyl-2-Hexenal, 5-Methyl-2-Thiophenecarboxaldehyde, 6-Methyl-3,5-Heptadien-2-One, 2-Methyl-3-(para-Isopropylphenyl) Propionaldehyde, 5-Methyl-3-Hexen-2-One, 1-Methyl-3-Methoxy-4-Isopropylbenzene, 4-Methyl-3-Pentene-2-One, 2-Methyl-4-Phenylbutylaldehyde, 6-Methyl-5-Hepten-2-One, 4-Methyl-5-Thiazolethanol, 4-Methyl-5-Vinylthiazole, Methyl-alpha-Ionone, Methyl-trans-2-Butenoic Acid, 4-Methylacetophenone, para-Methylanisole, alpha-Methylbenzyl Acetate, alpha-Methylbenzyl Alcohol, 2-Methylbutylaldehyde, 3-Methylbutylaldehyde, 2-Methylbutyric Acid, alpha-Methylcinnamaldehyde, Methylcyclopentenolone, 2-Methylheptanoic Acid, 2-Methylhexanoic Acid, 3-Methylpentanoic Acid, 4-Methylpentanoic Acid, 2-Methylpyrazine, 5-Methylquinoxaline, 2-Methyltetrahydrofuran-3-One, (Methylthio)Methylpyrazine (Mixture Of Isomers), 3-Methylthiopropionaldehyde, Methyl 3-Methylthiopropionate, 2-Methylvaleric Acid, Mimoso Absolute and Extract, Molasses Extract and Tincture, Mountain Maple Solid Extract, Mullein Flowers, Myristaldehyde, Myristic Acid, Myrrh Oil, beta-Naphthyl Ethyl Ether, Nerol, Neroli Bigarde Oil, Nerolidol, Nona-2-trans,6-cis-Dienal, 2,6-Nonadien-1-Ol, gamma-Nonalactone, Nonanal, Nonanoic Acid, Nonanone, trans-2-Nonen-1-Ol, 2-Nonenal, Nonyl Acetate, Nutmeg Powder and Oil, Oak Chips Extract and Oil, Oak Moss Absolute, 9,12-Octadecadienoic Acid (48%) And 9,12,15-Octadecatrienoic Acid (52%), delta-Octalactone, gamma-Octalactone, Octanal, Octanoic Acid, 1-Octanol, 2-Octanone, 3-Octen-2-One, 1-Octen-3-Ol, 1-Octen-3-Yl Acetate, 2-Octenal, Octyl Isobutyrate, Oleic Acid, Olibanum Oil, Opopanax Oil And Gum, Orange Blossoms Water, Absolute, and Leaf Absolute, Orange Oil and Extract, Origanum Oil, Orris Concrete Oil and Root Extract, Palmarosa Oil, Palmitic Acid, Parsley Seed Oil, Patchouli Oil, omega-Pentadecalactone, 2,3-Pentanedione, 2-Pentanone, 4-Pentenoic Acid, 2-Pentylpyridine, Pepper Oil, Black And White, Peppermint Oil, Peruvian (Bois De Rose) Oil, Petitgrain Absolute, Mandarin Oil and Terpeneless Oil, alpha-Phellandrene, 2-Phenethyl Acetate, Phenethyl Alcohol, Phenethyl Butyrate, Phenethyl Cinnamate, Phenethyl Isobutyrate, Phenethyl Isovalerate, Phenethyl Phenylacetate, Phenethyl Salicylate, 1-Phenyl-1-Propanol, 3-Phenyl-1-Propanol, 2-Phenyl-2-Butenal, 4-Phenyl-3-Buten-2-Ol, 4-Phenyl-3-Buten-2-One, Phenylacetaldehyde, Phenylacetic Acid, 1-Phenylalanine, 3-Phenylpropionaldehyde, 3-Phenylpropionic Acid, 3-Phenylpropyl Acetate, 3-Phenylpropyl Cinnamate, 2-(3-Phenylpropyl)Tetrahydrofuran, Phosphoric Acid, Pimenta Leaf Oil, Pine Needle Oil, Pine Oil, Scotch, Pineapple Juice Concentrate, alpha-Pinene, beta-Pinene, D-Piperitone, Piperonal, Pipsissewa Leaf Extract, Plum Juice, Potassium Sorbate, 1-Proline, Propenyloethanol, Propionic Acid, Propyl Acetate, Propyl para-Hydroxybenzoate, Propylene Glycol, 3-Propyridenephthalide, Prune Juice and Concentrate, Pyridine, Pyrroligoneous Acid And Extract, Pyrrole, Pyruvic Acid, Raisin Juice Concentrate, Rhodiol, Rose Absolute and Oil, Rosemary Oil, Rum, Rum Ether, Rye Extract, Sage, Sage Oil, and Sage Oleoresin, Salicylaldehyde, Sandalwood Oil, Yellow, Sclareolide, Skatole, Smoke Flavor, Snakeroot Oil, Sodium Acetate, Sodium Benzoate, Sodium Bicarbonate, Sodium Carbonate, Sodium Chloride, Sodium Citrate, Sodium Hydroxide, Solanone, Spearmint Oil, Styraz Extract, Gum and Oil, Sucrose Octaacetate, Sugar Alcohols, Sugars, Tagetes Oil, Tannic Acid, Tartaric Acid, Tea Leaf and Absolute, alpha-Terpineol, Terpinolene, Terpinyl Acetate, 5,6,7,8-Tetrahydroquinoxaline, 1,5,5,9-Tetramethyl-13-Oxatricyclo(8.3.0.0(4,9))Tridecane, 2,3,4,5, and 3,4,5,6-Tetramethylthyl-Cyclohexanone, 2,3,5,6-Tetramethylpyrazine, Thiamine Hydrochloride, Thiazole, 1-Threonine, Thyme Oil, White and Red, Thymol, Tobacco Extracts, Tochopherols (mixed), Tolu Balsam Gum and Extract, Tolualdehydes, para-Tolyl-3-Methylbutyrate, para-Tolyl Acetaldehyde, para-Tolyl Acetate, para-Tolyl Isobutyrate, para-Tolyl Phenylacetate, Triacetin, 2-Tridecanone, 2-Tridecenal, Triethyl Citrate, 3,5,5-Trimethyl -1-Hexanol, para,para,alpha-Trimethylbutyl Alcohol, 4-(2,6,6-Trimethylcyclohex-1-Enyl)But-2-En-4-One, 2,6,6-Trimethylcyclohex-2-En-1,4-Dione, 2,6,6-Trimethylcyclohexa-1,3-Dienyl Methan, 4-(2,6,6-Trimethylcyclohexa-1,3-Dienyl)But-2-En-4-One, 2,2,6-Trimethylcyclohexanone, 2,3,5-Trimethylpyrazine, 1-Tyrosine, delta-Undercalactone, gamma-Undecalactone, Undecanal, 2-Undecanone, 1, 0-Undecenal, Urea, Valencene, Valeraldehyde, Valerian Root Extract, Oil and Powder, Valeric Acid, gamma-Valerolactone, Valine, Vanilla Extract And Oleoresin, Vanillin, Veratraldehyde, Vetiver Oil, Vinegar, Violet Leaf Absolute, Walnut Hull Extract, Water, Wheat Extract And Flour, Wild Cherry Bark Extract, Wine and Wine Sherry, Xanthan Gum, 3,4-Xylenol, Yeast

Smoking/Tobacco Related Cancers

- Head and neck
 - 90% of cases
- Lung
 - 80-90% of cases
- Esophagus
- Gastric
 - 1.5-3 fold increased risk
- Pancreas
 - 2 fold increased risk
- Colorectal
 - 2.5 fold increased risk
- Hepatobiliary
- Bladder
 - 50% of cases
- Renal
- Cervix
 - 2 fold increased risk
- Vulvar
- Vaginal
- Anal
- Leukemia

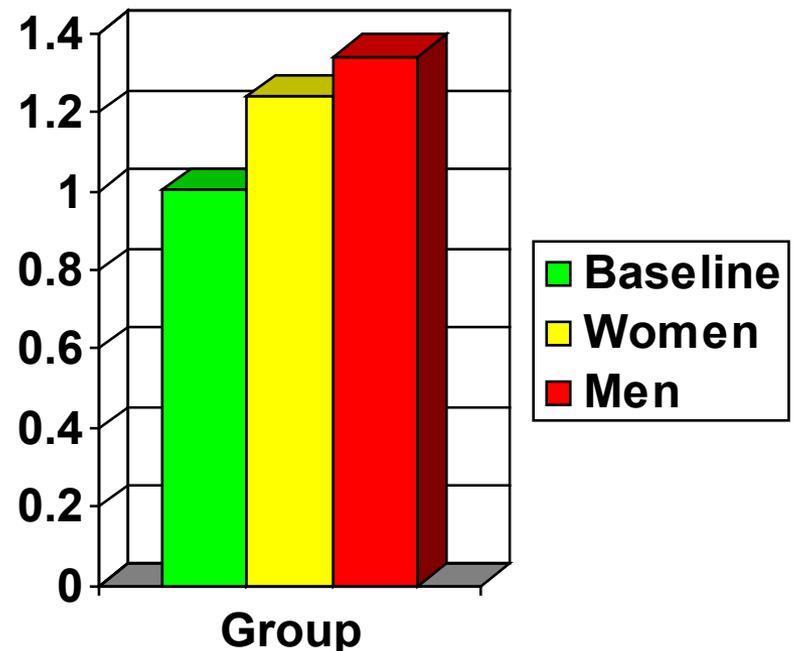


*Age-adjusted to 2000 US standard population.
 Source: Death rates: US Mortality Public Use Tapes, 1960-2000, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002.
 Cigarette consumption: US Department of Agriculture, 1900-2000.

Environmental Tobacco Smoke Exposure and Lung Cancer Risk

- Review of 37 studies of women and 9 studies of men
 - All non-smokers with smoking spouse
 - 478,000 women and 118,000 men
 - Overall 24% increase in lung cancer risk in women
 - Overall 35% increase in lung cancer risk in men

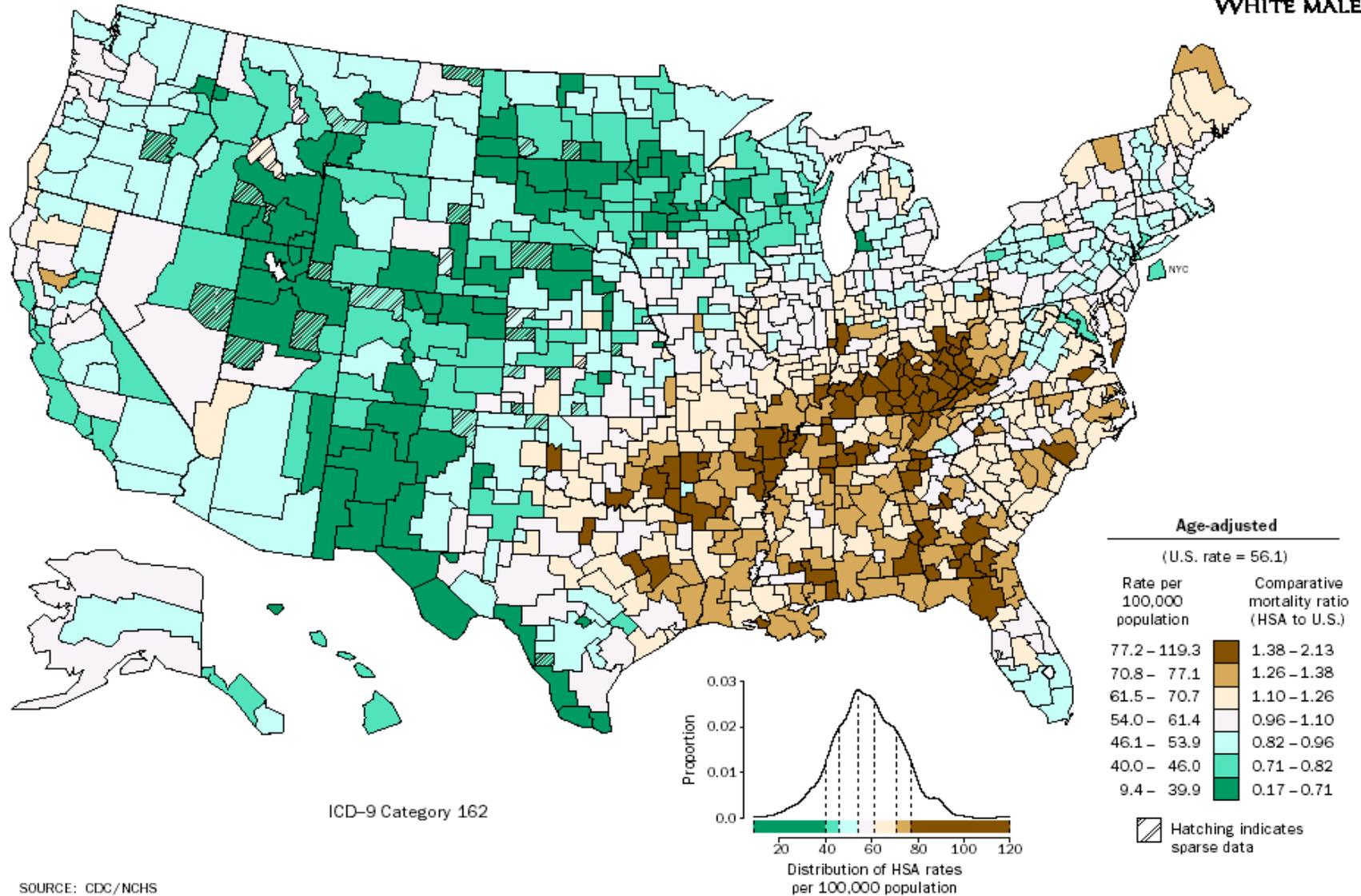
Relative Risk of Lung Cancer



Lung Cancer Death Rates

48 AGE-ADJUSTED DEATH RATES BY HSA, 1988-92

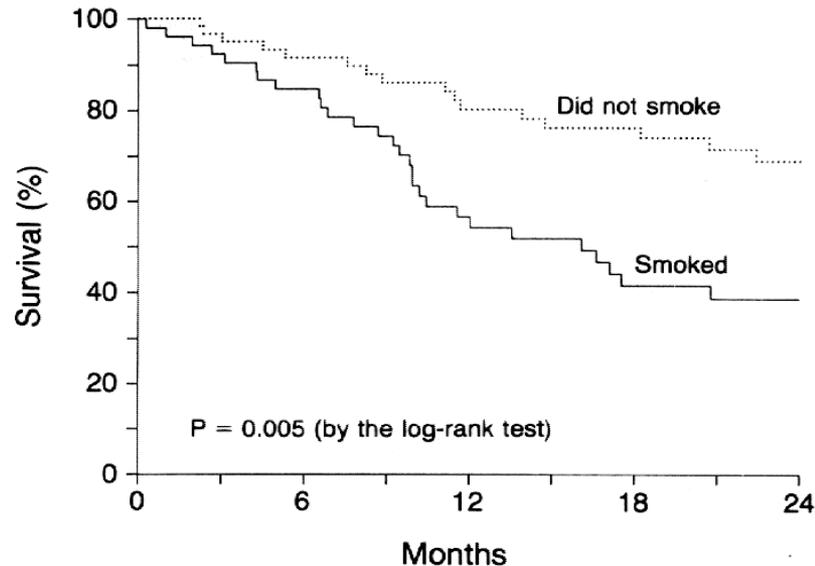
LUNG CANCER
WHITE MALE



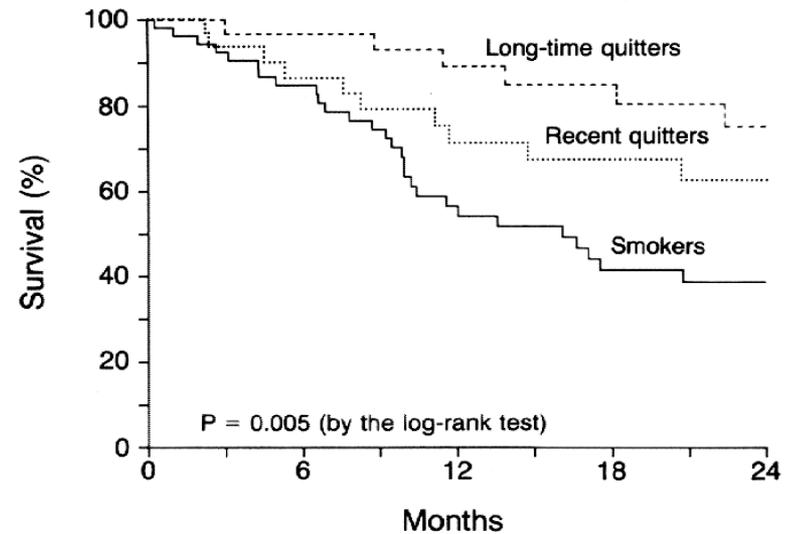
Habits Start Early



Smoking and Head/Neck Cancer Treatment



GROUP	0	6	12	18	24
Smoked	53	49	43	36	24
Did not smoke	62	58	51	44	40

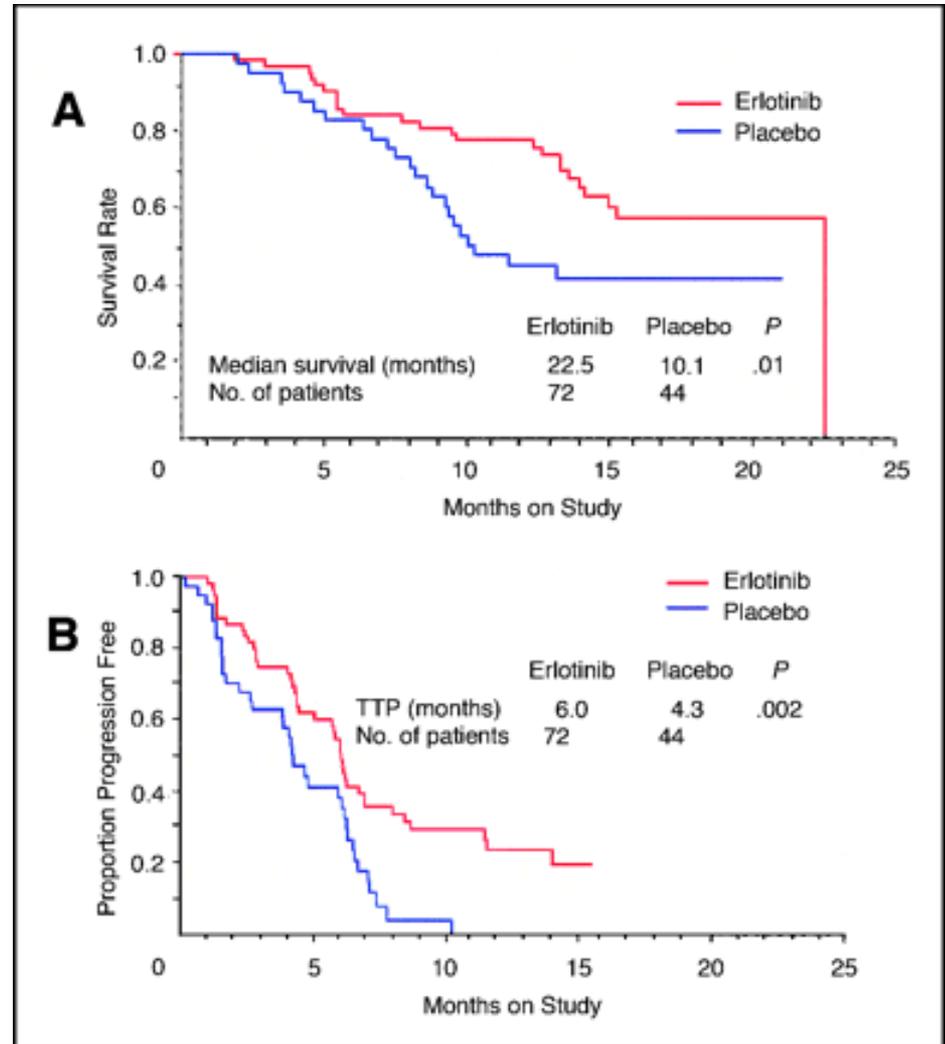


GROUP	0	6	12	18	24
Smokers	53	49	43	36	24
Recent quitters	32	28	24	20	18
Long-time quitters	30	30	27	24	22

- 115 Stage III-IV SCCA of H/N treated with XRT +/- fluorouracil
- 41% decrease in 2-year OS in patients who smoked during XRT
 - No difference based upon fluorouracil vs. placebo
 - No difference in toxicity (smokers during XRT vs. nonsmokers)

Smoking and Lung Cancer Treatment

- TRIBUTE trial of Tarceva in 1059 IIIB-IV NSCLC patients¹
 - No difference in overall patient cohort
 - Improved survival and time to progression in never smokers
- Gefitinib with improved survival in never-smokers²
 - 8.9 vs. 6.1 months



1. Herbst 2005 *J Clin Oncol* 23:5892, 2005

2. Thatcher *Lancet* 366:1527, 2005

Lung and Head/Neck Outcomes

Study	Population	Outcome (Smokers)
Rades <i>IJROBP</i> 71: 1134, 2008	NSCLC, 181 pts, RT +/- chemo	Decreased LRC
Tammemagi <i>Chest</i> 125: 27, 2004	Lung, 1155 pts.	Decreased survival
Hinds <i>J Nat Ca Inst</i> 68: 395, 1982	Lung, 223 women	Decreased 1-yr survival
Johnston-Early <i>JAMA</i> 244: 2175, 1980	SCLC, 112 pts, chemo +/- RT	Decreased survival
Stevens <i>Arch Oto</i> 109: 746, 1983	H/N, 269 pts.	Inc recurrence (75% less), dec survival
Rugg <i>Br J Radiol</i> 63: 554, 1990	H/N, 41 CHART pts.	Increased mucositis
Risch <i>Am J Epidem</i> 138: 281, 1993	Lung, 845 pts.	Women sm with higher risk vs. male sm
Phillips <i>Cancer</i> 56: 2789, 1985	Smokers, lung, 68 pts.	Decreased NK activity
Garces <i>Chest</i> 126: 1733, 2004	NSCLC, 1506 pts.	Decreased QOL
Pytina <i>J Clin Oncol</i> 22: 3981, 2004	H/N, 100 pts.	Decreased OS, RFS, DFS
Marin <i>Plast Recon Surg</i> 121: 451, 2008	H/N, 89 pts, flap recon	Poor wound healing (cor with cotinine)
Videtic <i>J Clin Oncol</i> 21: 1544, 2003	SCLC, 189 pts., chemo/RT	Decreased MS and 5-yr OS
Marshak <i>IJROBP</i> 43: 1009, 1999	Glottic larynx, 207 pts., RT	Decreased LRC (UV)
Fox <i>Lung Cancer</i> 44: 237, 2004	NSCLC, 237 pts, RT +/- chemo	Decreased MS and 2-yr survival (early stg)

Most of us agree on lung and H/N...
...what about other disease sites?

Gastrointestinal Outcomes

Study	Population	Outcome (Smokers)
Richards <i>Ann Surg</i> 254:83, 2011	423 rectal	C/F decrease CSS and OS, near decreased postop outcomes (p=0.09)
Phipps <i>Cancer</i> 117:4948, 2011	2264 CRC with follow-up 6.9 months after diagnosis	Current increase CSM (HR 1.3) and OM (HR 1.51)
Weaver <i>CEBP</i> 20: 239, 2011	743 CRC caregivers	Poor mental health in caregivers of cancer patients who smoke
Hawkes <i>Eur J Cancer</i> 47:267, 2010	1966 CRC survivors interviewed 5, 12, 24, 36, mo post diagnosis	Current increase DM (HR 3.11) and cholesterol (HR 4.07)
Roxburgh <i>Ann Surg Oncol</i> 2011 Richards <i>Br J Cancer</i> 103: 1356, 2010	302/320 CRC in surgical unit	C/F decrease OS (p=0.07), increase CCI, infection, inflam, cardiac risk
McCLeary <i>Cancer</i> 116: 957, 2010	1246 Stage III Colon 5FU+/- irinotecan (CALGB 89803)	Current decrease OS (HR 1.67)
Zingg <i>Ann Surg Oncol</i> 18:1460, 2011	858 esophagectomy pts	Increased pulm morbidity and pneumonia
Kelly <i>J Gastrointest Surg</i> 15:250, 2010	2322 dist pancreatectomy	Increased Sx morbidity (MV)
Kountourakis <i>Cancer</i> 117:925, 2011	49 T2N0 esoph pts (MDACC)	Decreased DFS and OS (UV, MV)
Shitara <i>Cancer Sci</i> 101:1001, 2010	364 SCC esoph	decrease survival (HR 2.43) esp. CRT
Cooke <i>Ann Thorac Surg</i> 88:177, 2009	1133 esophagectomy	Increased anastamotic leakage
Van der Heide <i>Liver Transp</i> 15:648, 2009	401 liver transplant pts	10-yr malig 13% active vs. 2% non-smok
Wright <i>J Thorac Cardiovasc Surg</i> 137:587, 2009	2315 esophagectomies from 73 centers	Increased major morbidity (leak, pneumonia, bleeding, vent, death)
Camargo <i>Acta Gast Lat</i> 37:238, 2007	264 precancerous w. H. Pylori	Decreased H. pylori eradication

Gynecologic Outcomes

Study	Population	Outcome (Smokers)
Kasuya <i>Anticancer Res</i> 31:3527, 2011	228 cervix/uterine, postop RT	Increased enterocolitis
Matsumoto <i>Cancer Sci</i> 101:2065, 2010	516 LG SIL followed for 2 yrs	Dec regression, inc persistent HPV
Jang <i>J Cancer Surv</i> 5:115, 2011	1920 br, CRC, Uterine survivors	Increased stroke, decreased activity+QOL
Ngô <i>Gynecol Oncol</i> 123:248, 2011	257 IB1-IIV cerv, preop brachy	Decreased 5-yr OS and DFS
Girianelli <i>Int J Gyn Obst</i> 107:228, 2009	1236 LG SIL, followed for 3 yrs	Increased progression to CIN2+
Khan <i>J Obst Gyn</i> 29:123, 2009	80 VIN3	Increased multicentric and persitent dz
Coker <i>Gynecol Oncol</i> 112:365, 2009	2661 cervical	Increased CSM
Simen <i>Scand J Infect Dis</i> 40:745, 2008	191 HPV infected women	Decreased antibodies to HPV 16/18
Ohno <i>IJROBP</i> 69:740, 2007	2167 cervical treated with RT	Increased second malignancy
Waggoner <i>Gynecol Oncol</i> 103:853, 2006	316 St IIB-IVA cervical, CRT (GOG 165)	Decreased OS and PFS Self-reported and cotinine validated
Modesitt <i>Gynecol Oncol</i> 103:300, 2006	3563 endometrial	Decreased survival
Wright <i>Gynecol Oncol</i> 98:84, 2005	255 IB-IIB cervical, prospective	Increase recurrence, CSM, OM
Eifel <i>J Clin Oncol</i> 20: 3651, 2002	3489 I-II cervical with RT	Increased bladder-bowel complication
Hsia <i>Prev Med</i> 31:261, 2000	55278 WHI non cancer women	Decreased mam/pap/FS screening
Maucort <i>Int J Cancer</i> 126:684, 2010	2408 women	Persistent HPV infection
Schlumbrecht <i>Cancer</i> 117:3741, 2011	194 low gr serous ovarian	Decrease OS and RFS
Kjaerbye <i>CEBP</i> 15:798, 2006	295 St III ovarian (MALOVA)	Increased mortality, improved with cess

Hematologic Outcomes

Study	Population	Outcome (Smokers)
Lieberman <i>Clin Vaccine Immunol</i> 15:49, 2008	72 non-cancer women	Decrease IL1B, IFN-g, IL-6, IL-10, and cytokines in cervical mucus
Varadarajan <i>Int J Cancer</i> 2011	180 AML	Increased mortality
Ehlers <i>BMT</i> 46:285, 2011	148 AML/ALL (Mayo)	Increased hospital stay/admit and mortality
Marks <i>Biol BMT</i> 15:1277, 2009	2818 CML	Increased treatment related mortality, decreased DFS and OS
Thomas <i>Cancer</i> 113:3248, 2008	74 long term ALL survivors	Decreased bone mineral density
Chang <i>Cancer</i> 101:782, 2004	114 allogenic stem cell txpl	1.7% increase in recurrence per PY
Chelghoum <i>Ann Oncol</i> 13:1621, 2002	643 AML	Dec DFS, OS, remission, Inc infection
Herr <i>Am J Hematol</i> 34:1, 1990	122 CML	Increased blast crisis, decreased OS
Archimbaud <i>Cancer</i> 63:2060, 1989	173 CML	Younger, early blast crisis, decreased OS
Thalamini <i>Int J Cancer</i> 122:1624, 2008	268 NHL	Decreased OS
Moser <i>Haematol</i> 91:1481, 2006	748 NHL	Increased second malignancy
Moser <i>Clin Lymphoma Myel</i> 6:122, 2005	757 aggressive NHL	Increased cardiovascular disease
Lorigan <i>Lancet Oncol</i> 6:773, 2005	19046 HD	Increased synerg risk of lung cancer with RT and/or alkylating agent

Genitourinary (non-prostate) Outcomes

Study	Population	Outcome (Smokers)
Park <i>J Clin Oncol</i> 24:5017, 2006	901879 males (Korean Natl Health Insurance Corp)	Current increase overall mortality in entire cohort
Lammers <i>Eur Urol</i> 60:713, 2011	718 NMIBC with epirubicin	Increased recurrence (UV, MV)
Boström <i>BJU Int</i> 2011	564 bladder, rad cyctectomy	Decreased 10-yr DSS and OS
Fleshner <i>Cancer</i> 86: 2337	268 transitional cell CA	Current decrease RFS
Yu <i>Cancer Detect Prev</i> 21:497, 1997	25436 tumor registry pts (MSK)	Ever decrease OS
Kroeger <i>Cancer</i> 2011	802 RCC	Ever increase DSM, OM
Richey <i>Ann Oncol</i> 22:1048, 2010	188 metastatic RCC, targeted tx	Current decrease survival (UV, MV)
Oh <i>Urology</i> 55:31, 2000	148 RCC	Ever decrease OS in metastatic pts
Van den Belt-Dusebout <i>J Clin Oncol</i> 25:4370, 2007	2707 testicular cancer survivors	Increased second malignancy (HR 1.8) and heart disease (HR 1.8), both (HR 3.4)
Shinn <i>Urology</i> 69:748, 2007	162 testicular cancer	Increased depressive symptoms
Van den Belt-Dusebout <i>J Clin Oncol</i> 24:467, 2006	2512 testicular 5 yr survivors	Increased myocardial infarction (HR 2.6)
Peat <i>Plast Reconstr Surg</i> 93:980, 1994	180 limb sarcoma	Increased wound complications (UV)
Hemmati <i>Eur J Card Surg</i> 40:328, 2011	79 chest wall resection	Decreased survival
Newcomer <i>J Surg Oncol</i> 103:85, 2011	77 thigh sarcoma	Increased all cause mortality

Prostate Outcomes

Study	Population	Outcome (Smokers)
Alsadius <i>Radiother Oncol</i> , 2011	834 prostate, tx with RT	Increased urgency, cramps, diarrhea
Kenfield <i>JAMA</i> 305:2548, 2011	Prospective 5366 prostate (Health Prof Follow-up Study)	Current increased overall, prostate, CVD mortality, reversed with 10+ yr cessation
Joshu <i>JNCI</i> 103:835, 2011	1416 prostatectomy	Current increase recurrence, cess by 1 yr post diagnosis with no increased risk
Chen <i>J Chin Med Assoc</i> 74:69, 2011	89 radiation enterocolitis pts	Increased need for surgery
Taira <i>IJROBP</i> 79:1336, 2011	1656 RT/brachy pts +/-ADT	Decrease OS (HR 2.9 curr, 1.4 former)
Ku <i>Can Urol Assoc J</i> 3:445, 2009	213 prostatectomy	Decreased QOL
Weinmann <i>Ca Caus Cont</i> 21:117, 2010	768 who died of prostate CA (Pros Ca Scr Mort Study)	Most recent smoking status most important predictor for prostate cancer death
Watters <i>CEBP</i> 18:2427, 2009	283312 men	Increased fatal prostate cancer (HR 1.7)
Huncharek <i>Am J Pub Hth</i> 100:693, 2010	24 cohort review	Increased prostate cancer and fatal PC
Shiels <i>Ca Caus Cont</i> 20:877, 2009	1275 non-cancer (NHANES III)	Increased serum+free testosterone
Simone <i>J Urol</i> 180:2447, 2008	5070 prostatectom (CaPSURE)	Increase non-prostate mortality
Bittner <i>IJROBP</i> 72:433, 2008	1354 brachy +/- ADT	Increased CVD and non-prostate mort
Boorjian <i>J Urol</i> 177:883, 2007	9780 prostate (CaPSURE)	Increased bladder CA esp. current sm+RT
Carlos <i>J Am Coll Surg</i> 200:216, 2005	22094 non-cancer men	Decreased CRC and prostate screening

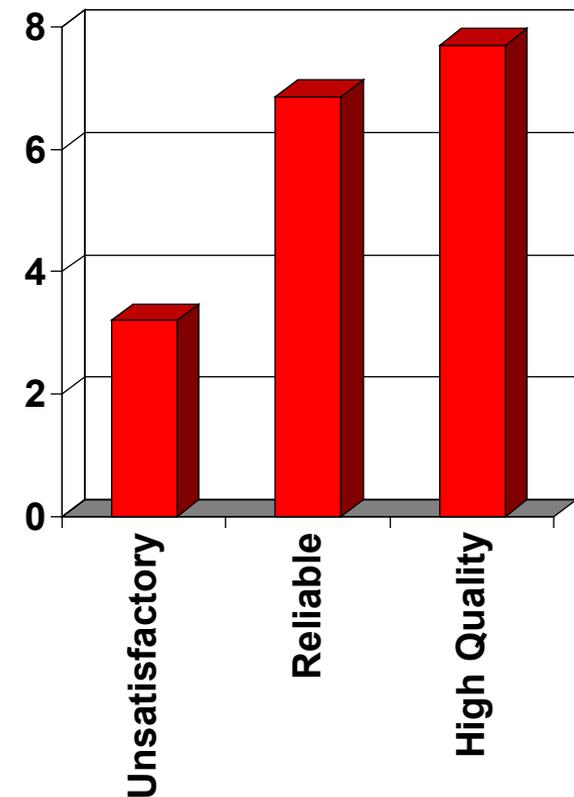
Breast Outcomes

Study	Population	Outcome (Smokers)
Angarita <i>J Hosp Infect</i> 79:328, 2011	199 breast cancer	Increased postop infection
Zaman <i>Ann Oncol</i> 2011	261 tam/let breast (BIG 1-98)	Decreased bone mineral density
Land <i>Ca Prev Res</i> 4:1393, 2011	NSABP P-1 (prevention)	Decreased adherence to tamoxifen
Hellmann <i>Eur J Ca Prev</i> 19:366, 2010	528 breast (Copen Ht St)	Increased mortality
Baumann <i>Plas Rec Surg</i> 125:1335, 2010	228 br recon, prosp (MDACC)	Increased fat necrosis
Dragun <i>Cancer</i> 117:2590, 2011	11914 Tumor registry	Decreased OS
Cowen <i>Br Ca Res Treat</i> 121:627, 2010	141 postop recon, (prospective)	Increased implant failure
Li <i>J Clin Oncol</i> 27:5312, 2009	1089 unilateral ER+ breast	Increased contralateral breast CA
Stefan <i>J Neurooncol</i> 94:221, 2009	1274 stroke unit pts (+/- Ca)	Increased thrombosis, similar stroke risk as in non-cancer patients
Wadhwa <i>Br Ca Res Treat</i> 117:357, 2009	152 trazituzumab pts	Increased cardiomyopathy risk (~5 fold)
Dal Maso <i>Int J Cancer</i> 123:2188, 2008	1453 breast	Increased OM and DSM
McCarthy <i>Plas Rec Surg</i> 121:1886, 2008	1170 breast, surgery (MSK)	Increased complications and recon failure
Sagiv <i>JNCI</i> 99:365, 2007	1273 breast with post dx assess	Increased OM and DSM
Jagsi <i>Cancer</i> 109:650, 2007	828 breast, sx+RT	Increased MI and MI req intervention
Sorenson <i>Eur J Surg Oncol</i> 28:815, 2002	415 mastectomy (prospective)	Increased infection, necrosis, epidermolysis

Tobacco, Data Quality, and Analysis

- Meta-analysis of 6 cohort and 24 case-control studies for smoking and pancreatic cancer risk¹
 - Risk ratios changed based upon quality of data collection
- Variable combinations or definitions of tobacco alter interpretation of outcomes^{3,4}

OR for bladder cancer risk in 2490 patients²



1. La Torre *Pancreas* 38:241, 2009
2. Villanueva *CEBP* 18:1312, 2009
3. Lee *BMC Cancer* 9:256, 2009
4. Parsons *BMJ* 340, 2009

Smoking at Diagnosis and Survival

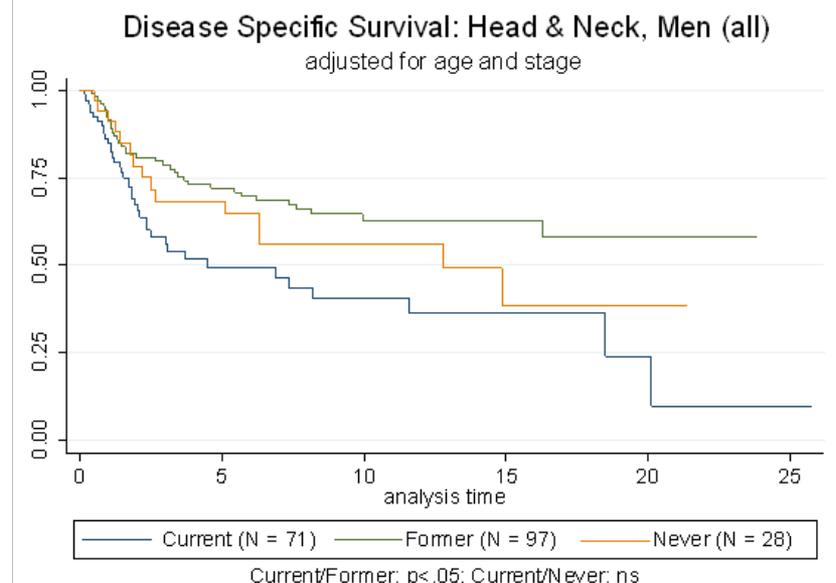
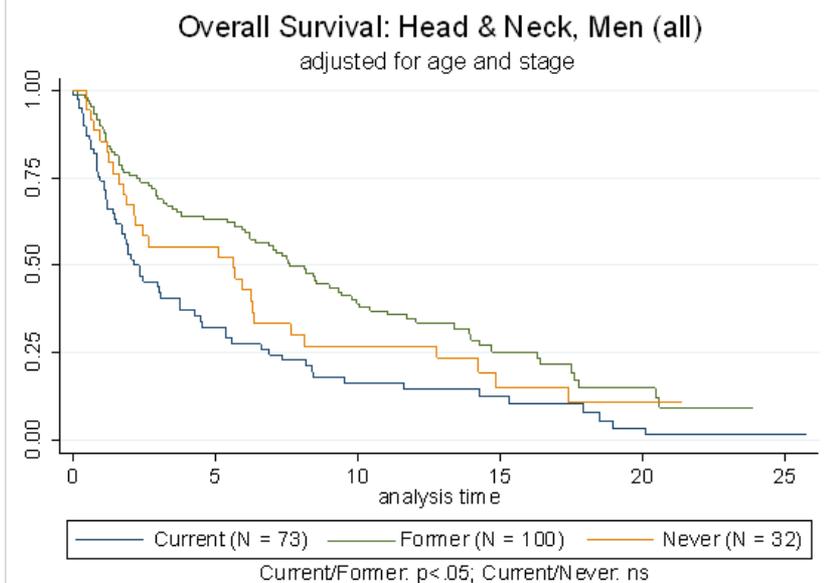
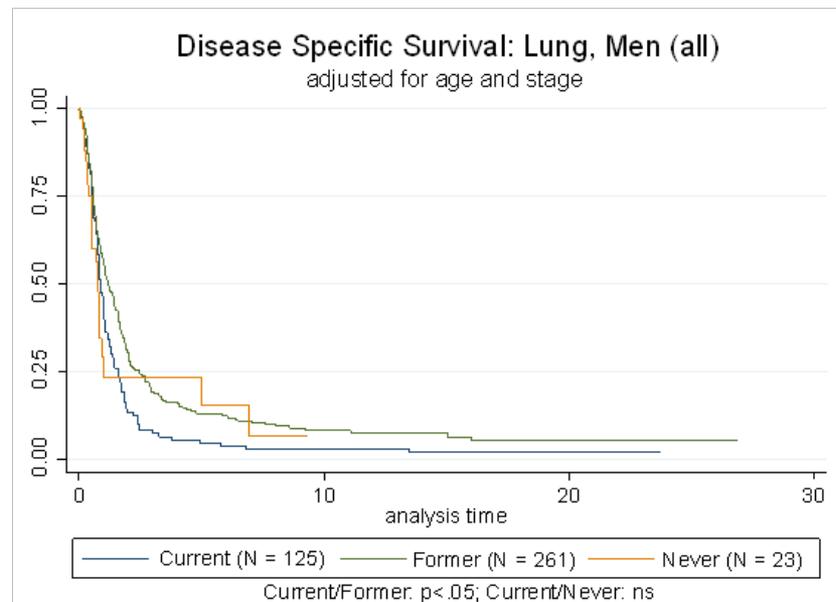
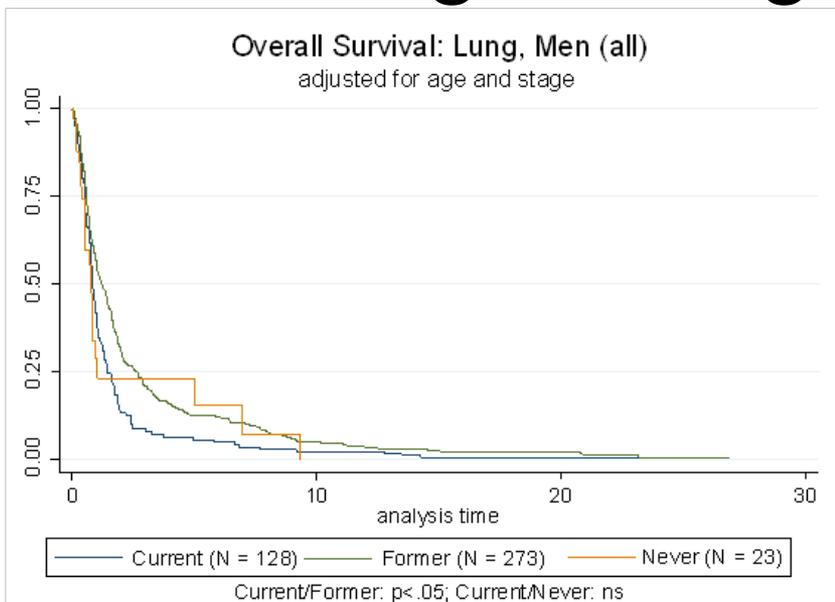
- Prospective structured assessment of tobacco at diagnosis in 5185 cancer patients from 13 disease sites
 - 1982-98 with 12-year minimum follow-up (up to 27.7 years)
 - Model 1: disease site, sex, age and stage
 - Model 2: Model 1 + race, date of diagnosis, BMI at diagnosis and total pack-years of smoking

Type of analysis (sample size for each group)	Current versus recent quit				Current versus former				Current versus never			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	HR/OR	(95% CI)	HR/OR	(95% CI)	HR/OR	(95% CI)	HR/OR	(95% CI)	HR/OR	(95% CI)	HR/OR	(95% CI)
Cox proportional hazards: OM (C = 915, RQ = 522, F = 1817, N = 1931)	1.18	(1.04, 1.33)	1.17	(1.03, 1.32)	1.30	(1.18, 1.33)	1.29	(1.17, 1.42)	1.38	(1.24, 1.53)	1.38	(1.23, 1.54)
Cox proportional hazards: DSM (C = 881, RQ = 500, F = 1733, N = 1831)	1.10	(0.95, 1.27)	1.08	(0.94, 1.25)	1.24	(1.10, 1.39)	1.23	(1.09, 1.39)	1.19	(1.04, 1.36)	1.18	(1.03, 1.36)
Logistic Regression: 3-year OM (C = 908, RQ = 522, F = 1813, N = 1917)	1.17	(0.88, 1.56)	1.17	(0.87, 1.57)	1.48	(1.19, 1.84)	1.50	(1.19, 1.89)	1.43	(1.13, 1.81)	1.45	(1.14, 1.85)
Logistic Regression: 3-year DSM (C = 866, RQ = 498, F = 1721, N = 1858)	1.21	(0.89, 1.64)	1.21	(0.89, 1.65)	1.54	(1.22, 1.95)	1.57	(1.22, 2.01)	1.40	(1.09, 1.80)	1.43	(1.10, 1.84)
Logistic Regression: 5-year OM (C = 905, RQ = 522, F = 1797, N = 1896)	1.20	(0.90, 1.59)	1.18	(0.88, 1.58)	1.34	(1.08, 1.66)	1.31	(1.05, 1.64)	1.50	(1.20, 1.88)	1.53	(1.22, 1.93)
Logistic Regression: 5-year DSM (C = 841, RQ = 484, F = 1663, N = 1804)	1.25	(0.91, 1.70)	1.24	(0.90, 1.70)	1.34	(1.06, 1.69)	1.34	(1.05, 1.71)	1.41	(1.11, 1.79)	1.43	(1.12, 1.83)

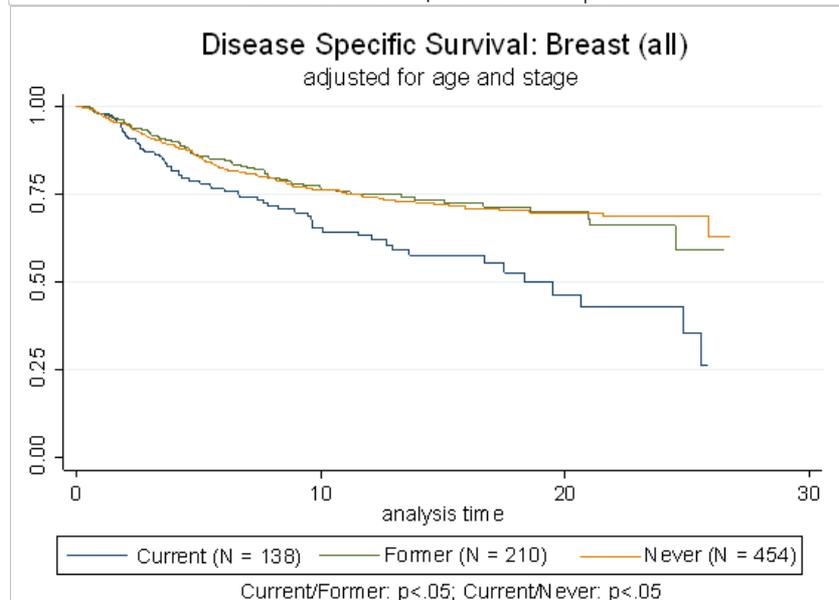
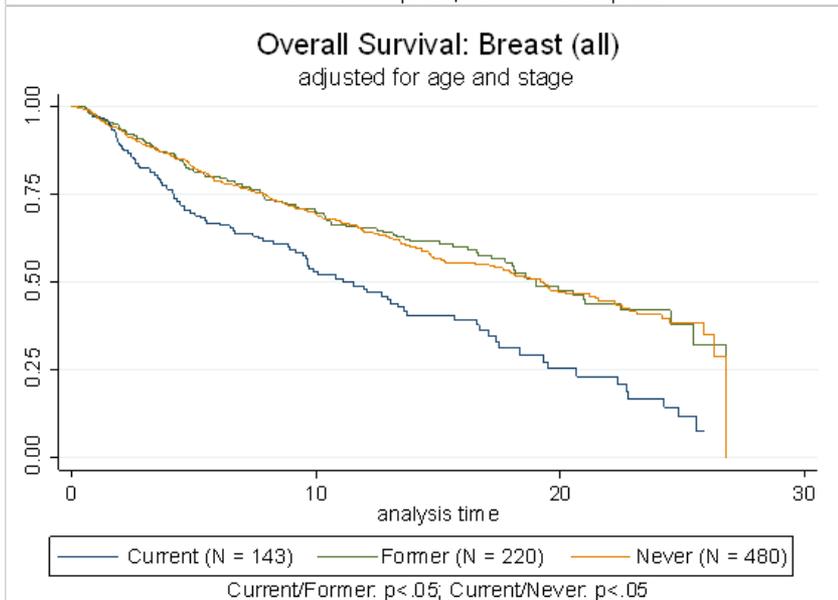
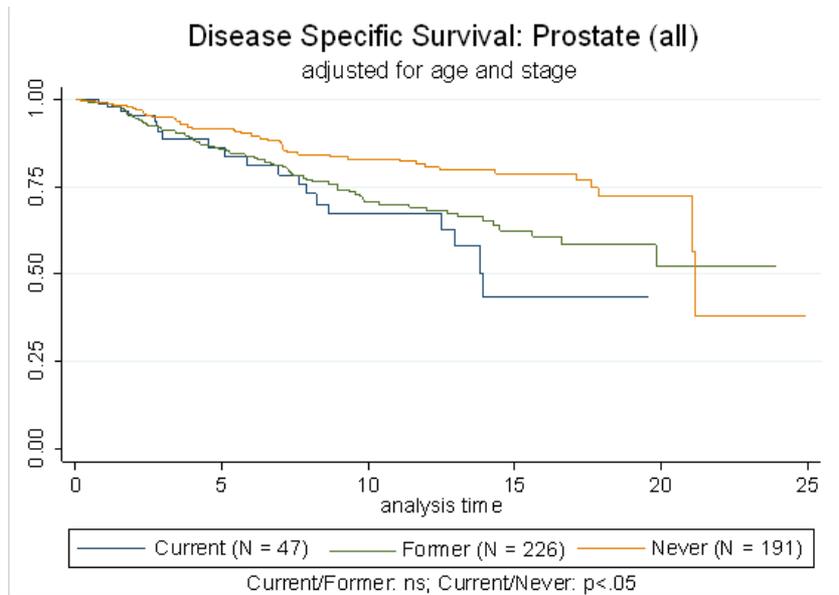
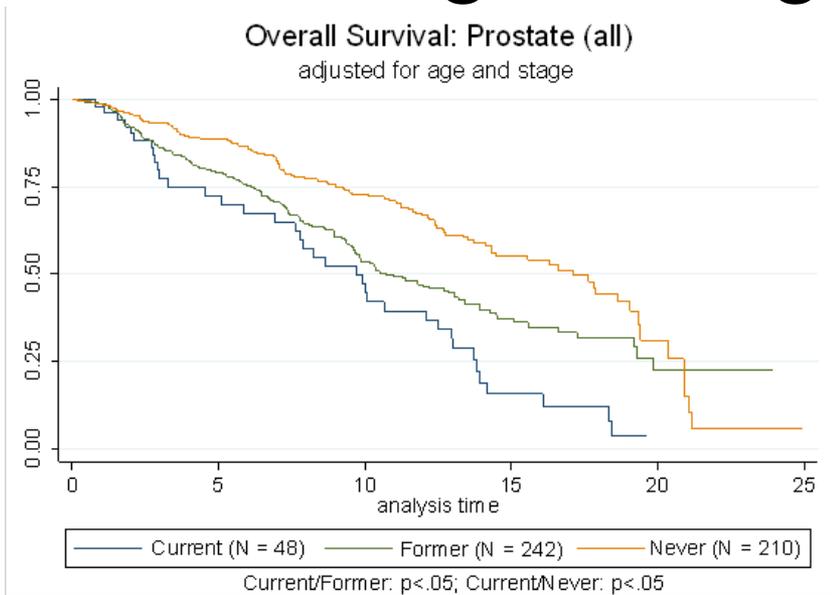
Hazard/odds ratios were calculated using adjustments for Model 1 and Model 2.

Abbreviations: C, current smoker; RQ, recent quit; F, former smoker; N, never smoker, HR, hazard ratio; OR, odds ratio; OM, overall mortality; DSM, disease-specific mortality; CI, confidence interval.

Smoking at Diagnosis and Survival



Smoking at Diagnosis and Survival



Survival in Current vs. Recent Quit

Men

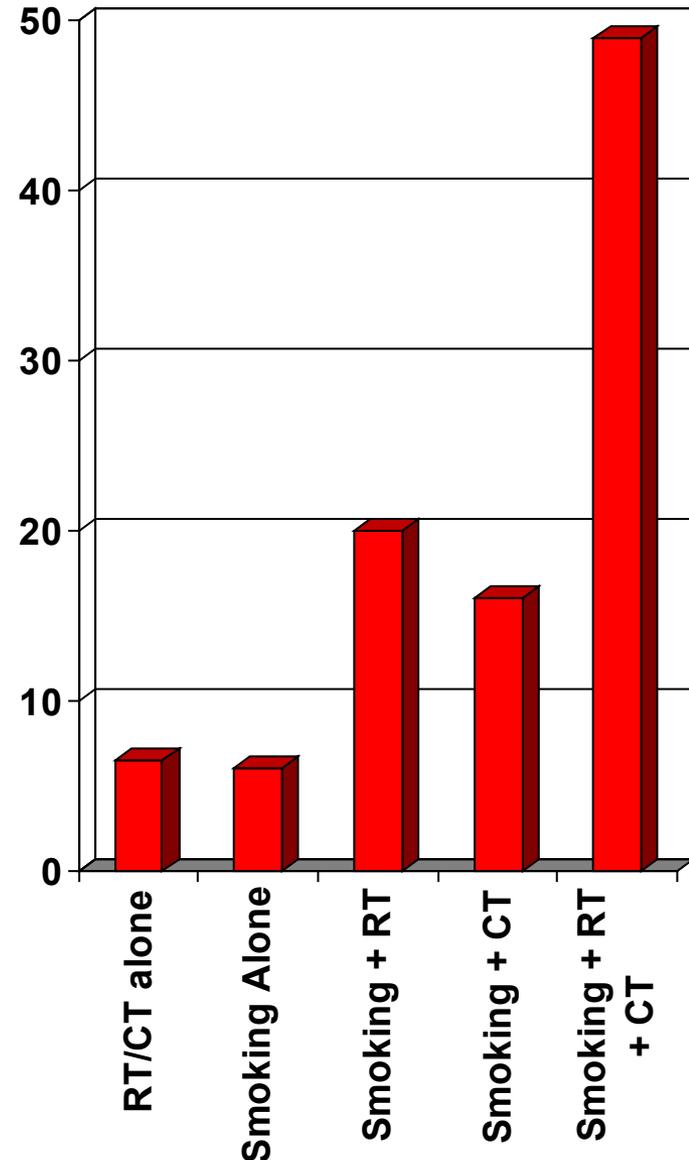
Disease site	Current versus recent quit			
	Model 1		Model 2	
	HR	(95% CI)	HR	(95% CI)
Overall mortality				
Lung	1.40	(1.09, 1.80)	1.38	(1.06, 1.79)
Head and neck	2.11	(1.41, 3.14)	2.15	(1.42, 3.25)
Bladder	-	-	-	-
Colon/rectum	-	-	-	-
Prostate	0.84	(0.42, 1.69)	0.83	(0.41, 1.68)
Leukemia	1.70	(0.73, 3.92)	1.52	(0.65, 3.58)
Melanoma	-	-	-	-
Disease-specific mortality				
Lung	1.32	(1.02, 1.72)	1.29	(0.99, 1.69)
Head/neck	2.10	(1.21, 3.64)	2.01	(1.15, 3.48)
Bladder	-	-	-	-
Colon/rectum	-	-	-	-
Prostate	0.68	(0.27, 1.70)	0.64	(0.25, 1.61)
Leukemia	1.95	(0.79, 4.83)	1.72	(0.68, 4.37)
Melanoma	-	-	-	-

Women

Disease site	MP	Current versus recent quit			
		Model 1		Model 2	
		HR	(95% CI)	HR	(95% CI)
Overall mortality					
Lung	All	0.95	(0.72, 1.26)	0.97	(0.73, 1.29)
Head/neck	All	0.56	(0.32, 0.99)	0.51	(0.29, 0.92)
Colon/rectum	All	1.15	(0.48, 2.75)	0.84	(0.30, 2.29)
Breast	All	1.11	(0.70, 1.78)	1.02	(0.63, 1.63)
	Pre-	1.02	(0.55, 1.88)	0.90	(0.48, 1.67)
	Post-	1.23	(0.59, 2.55)	1.17	(0.56, 2.45)
Leukemia	All	0.45	(0.20, 1.02)	0.40	(0.17, 0.92)
Melanoma	All	0.99	(0.33, 2.98)	1.17	(0.31, 4.33)
	Pre-	1.29	(0.36, 4.69)	1.51	(0.34, 6.67)
Ovary	All	1.52	(0.72, 3.23)	1.64	(0.77, 3.53)
	Post-	2.72	(1.04, 7.04)	3.85	(1.36, 10.87)
Uterus	All	1.47	(0.58, 3.70)	1.38	(0.54, 3.50)
	Post-	-	-	-	-
Disease-specific mortality					
Lung	All	0.86	(0.63, 1.17)	0.87	(0.64, 1.18)
Head and neck	All	0.54	(0.25, 1.17)	0.46	(0.20, 1.02)
Colon and Rectum	All	1.21	(0.42, 3.44)	1.18	(0.34, 4.05)
Breast	All	1.10	(0.62, 1.94)	1.05	(0.59, 1.87)
	Pre-	1.18	(0.59, 2.37)	1.07	(0.53, 2.18)
	Post	1.07	(0.40, 2.85)	0.99	(0.37, 2.68)
Leukemia	All-	0.63	(0.26, 1.51)	0.67	(0.27, 1.66)
Melanoma	All	0.73	(0.19, 2.90)	0.62	(0.13, 2.96)
Ovary	All	1.73	(0.75, 3.98)	1.81	(0.77, 4.22)
	Post-	3.50	(1.18, 10.31)	4.31	(1.39, 13.51)
Uterus	All	4.90	(0.56, 43.48)	3.68	(0.41, 33.33)

Smoking, Hodgkins, and Lung Cancer

- Risk of lung cancer in 19,046 HD patients
 - In former smokers
 - HR for lung cancer 4-9
 - In current smokers
 - HR 6 with smoking
 - HR 20 with smoking + radiotherapy (RT)
 - HR 16 with smoking + alkylating agent (AA)
 - HR 49 with smoking + RT + AA

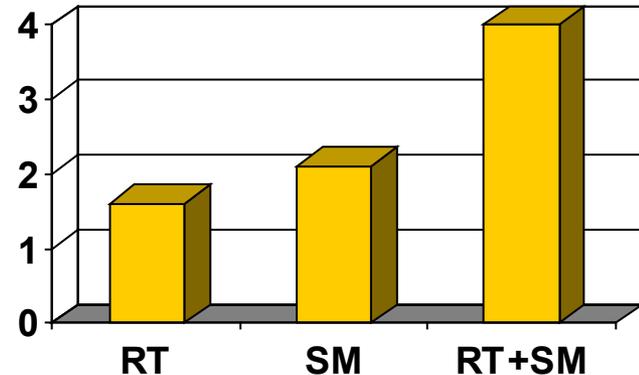


1. Lorigan *Lancet Oncol* 6:773, 2005

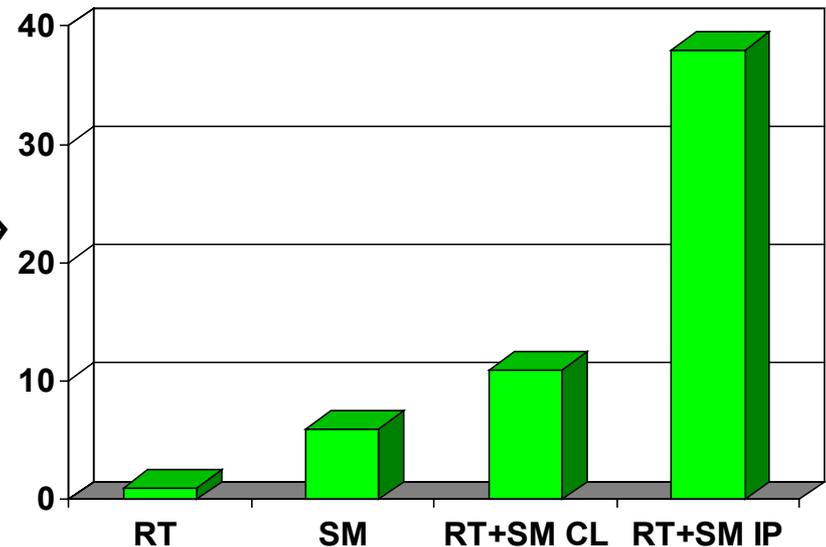
2. Travis *J Natl Cancer Inst* 94:182, 2002

Prostate, Breast, and 2nd Malignancy

- Bladder cancer risk in 9780 prostate cancer patients (CaPSURE)¹
 - HR 1.6 with RT alone
 - HR 2.1 with smoking
 - HR 4 with smoking + RT



- Lung cancer risk in 477 breast cancer patients (Conn)²
 - RT alone no increased risk
 - HR 6 with smoking alone
 - HR 19 (11 cont., 38 ips.) with smoking + RT



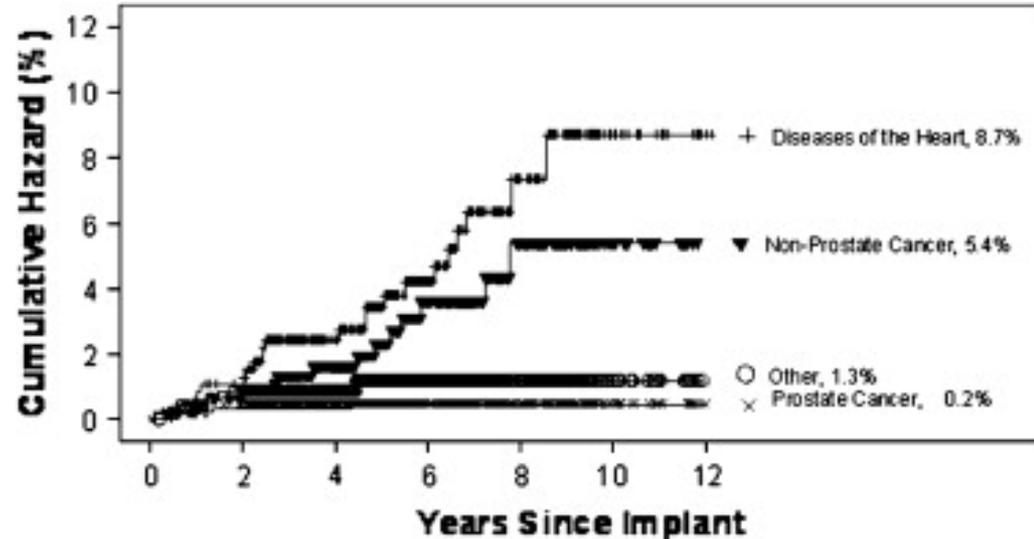
1. Boorjian *J Urol* 177:883, 2007

2. Kaufman *J Clin Oncol* 26:392, 2008

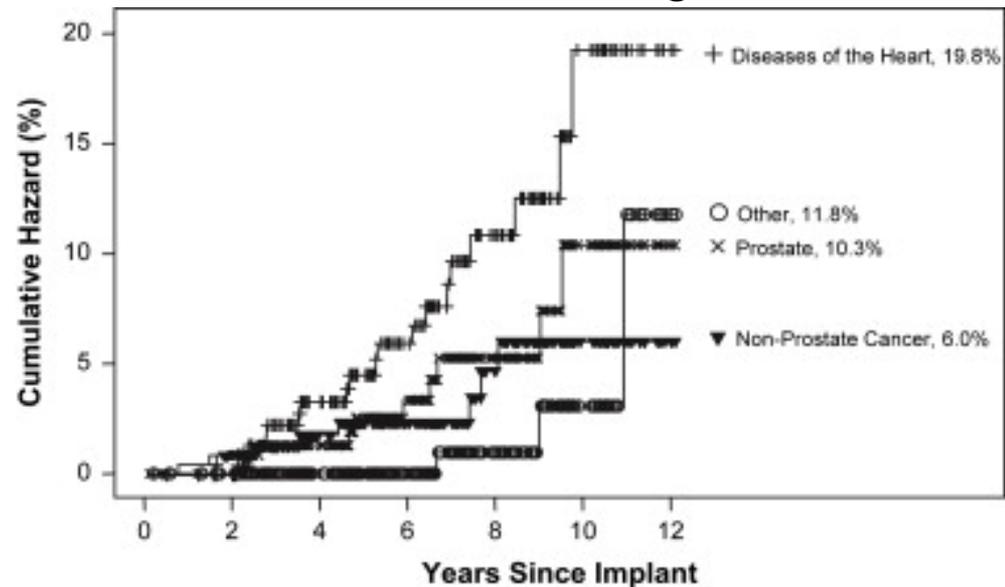
The Bigger Picture

- 1354 prostate patients treated with brachtherapy +/- androgen deprivation (1995-2004)
 - 475 low risk
 - 636 intermediate risk
 - 243 high risk

Cause of Death in Low Risk Pts



Cause of Death in High Risk Pts



The Bigger Picture

Cause of Death	% of Total Deaths	HR for Current Smokers
Cardiopulmonary disease	50.3%	3.05
Other	15.5%	5.52
Gastrointestinal cancer	12.4%	4.09
Lung cancer	9.9%	
Other cancers	3.1%	
Prostate cancer	8.7%	

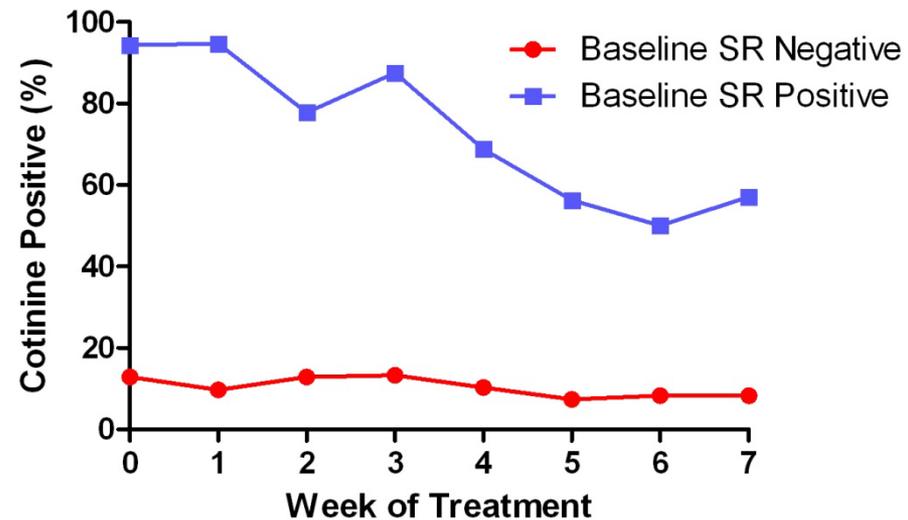
Treatment (surgery, radiotherapy, androgen deprivation and duration) all focus on optimizing a relatively low percentage of deaths

What about the larger percentage?

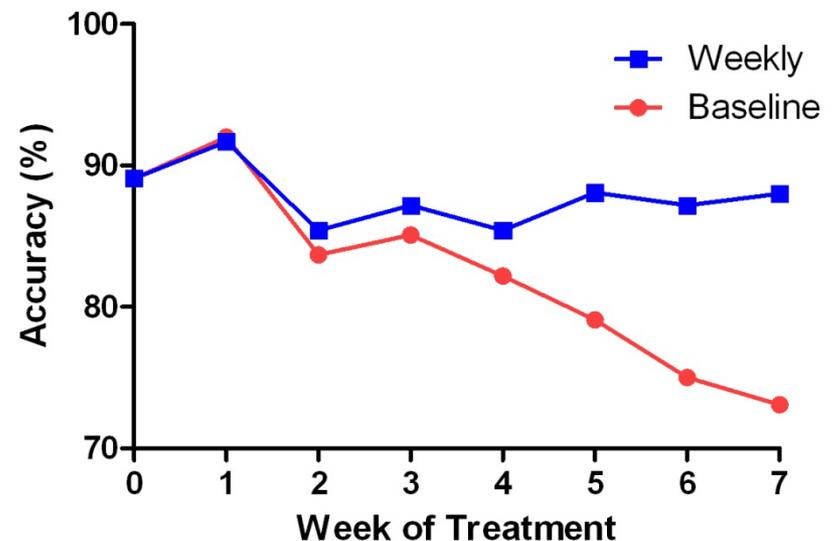
Self Reported Tobacco Use

- Head/neck cancer patients during RT/CRT¹
 - 29.4% of tobacco users required biochemical confirmation to accurately identify tobacco use
- Cotinine confirmed tobacco use in 39% of recent quitters in 1191 patient retinoid prevention trial²

Weekly Serum Cotinine in Patients Based upon Self-Report Status at Study Entry



Accuracy of Self-Reported Tobacco Use With Baseline or Weekly Assessments



1. Warren *Radiother Oncol* 103:45,2012

2. Khuri *Cancer Epid Biomarkers Prev* 10:823, 2001

False Reporting Rates

(newly diagnosed cancer patients)

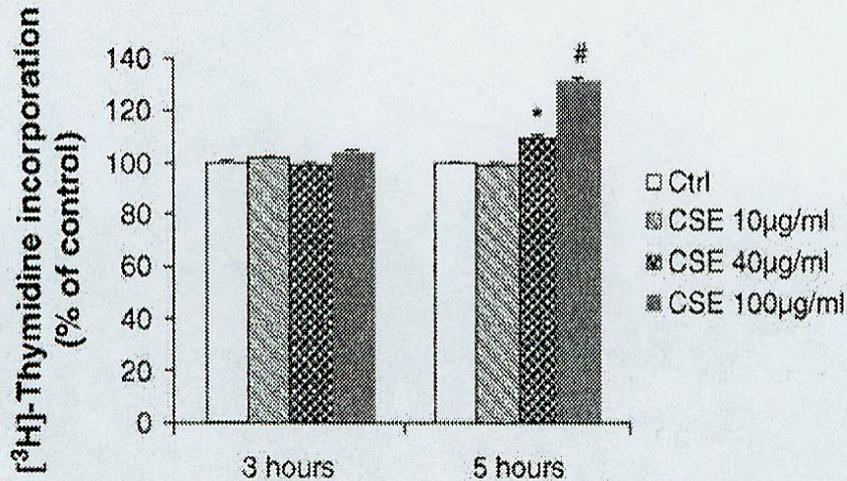
	Lung	Breast	Prostate	Overall
Current	0% (n=10)	0% (n=10)	0% (n=10)	0% (n=30)
Recent Quit	55.6% (n=27)	27% (n=27)	0% (n=11)	35.4% (n=65)
Former	0% (n=30)	0% (n=30)	6.3% (n=48)	2.8% (n=108)
Never	0% (n=10)	0% (n=10)	0% (n=10)	0% (n=30)

Summary of Clinical Outcomes

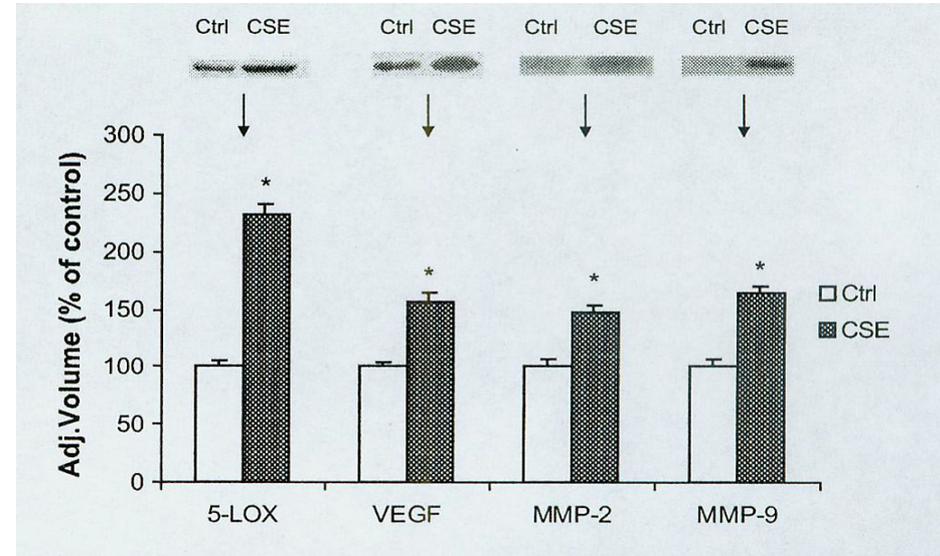
- Increased treatment toxicity and morbidity
 - Wound healing, necrosis, fibrosis, mucositis, infection, hematologic
 - Cardiovascular, pulmonary, cerebrovascular disease
 - Second malignancy
- Decreased quality of life
 - Fatigue, activity, depression, anxiety
- Decreased treatment compliance
- Decreased tumor control
- Decreased cancer specific survival
- Decreased non-cancer survival

All of these are likely underestimated...

Effect of Smoke on Cell Proliferation, VEGF, and MMP



Cigarette smoke extract (CSE) increased proliferation of SW1116 colon cancer cells



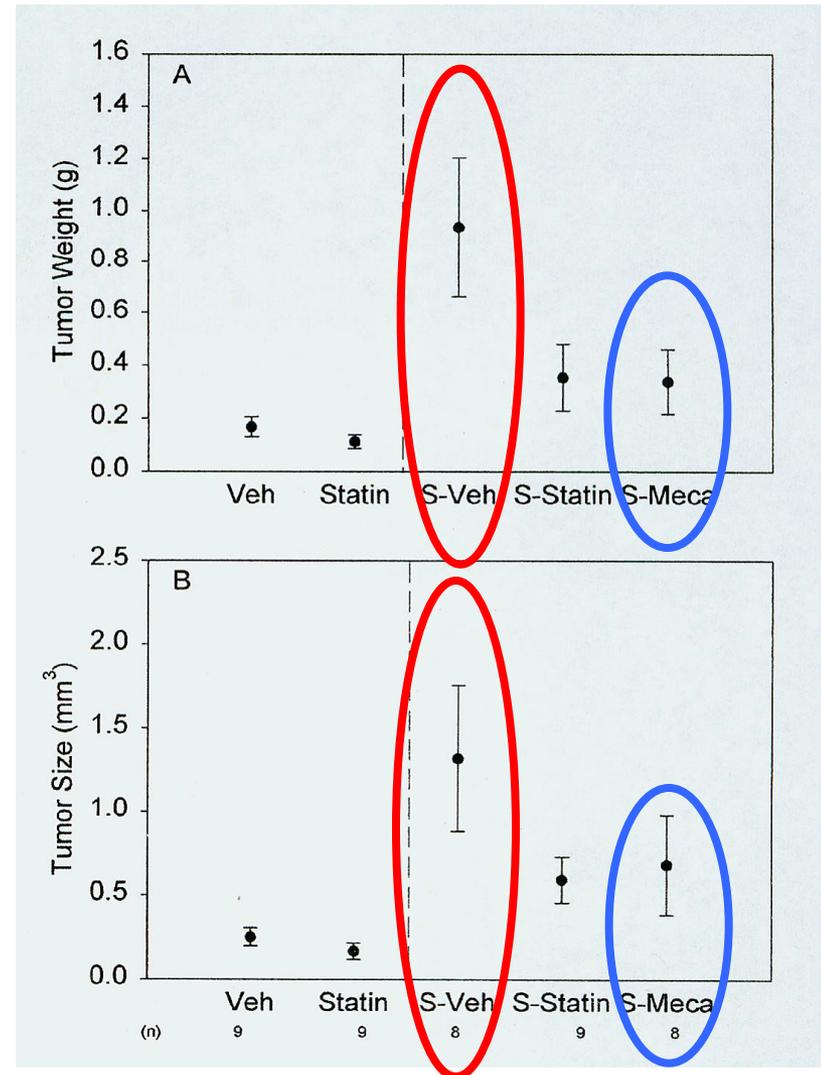
CSE increased VEGF and MMP in colon cancer cells

Note: Induction of vascular endothelial proliferation dependent upon presence of colon cancer cells and partially inhibited with VEGF and MMP inhibition

Effects of Secondhand Smoke on Tumor Progression

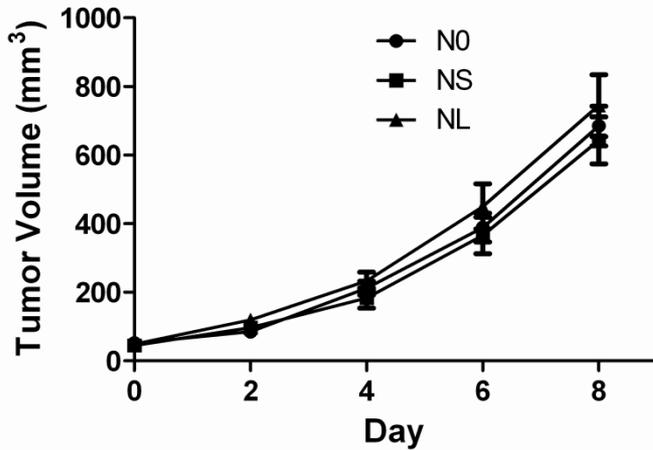
- Lewis lung cancer cells implanted into C57/BL6 mice
- Treated with secondhand smoke (inhalation chamber) in presence or absence of mecamylamine
 - Nonspecific nicotinic acetylcholine receptor (nAChR) inhibitor
- Inhibition prevented tumor growth induced by secondhand smoke
 - nAChR inhibition also prevented VEGF production and increased capillary density induced by smoke

Zhu *Cancer Cell* 4:191, 2003

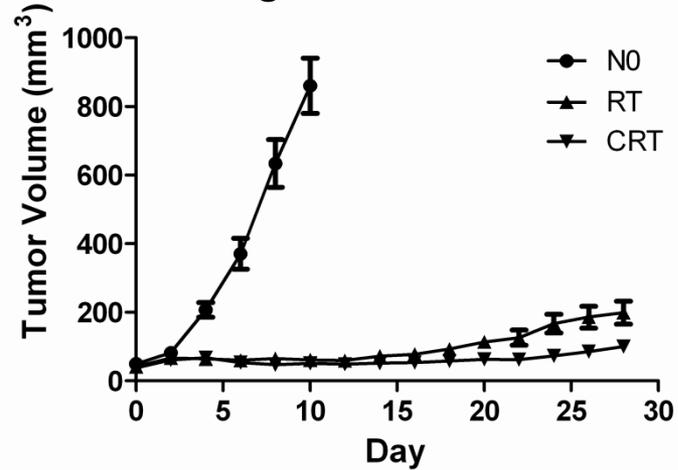


Therapeutic Response *In Vivo*

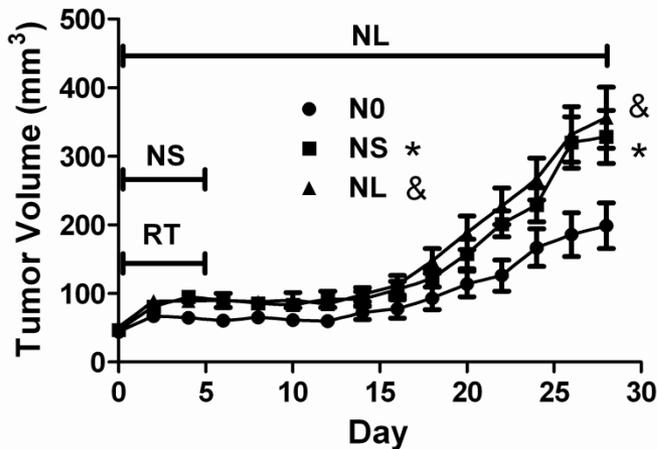
A. Effect of Nicotine on Tumor Growth



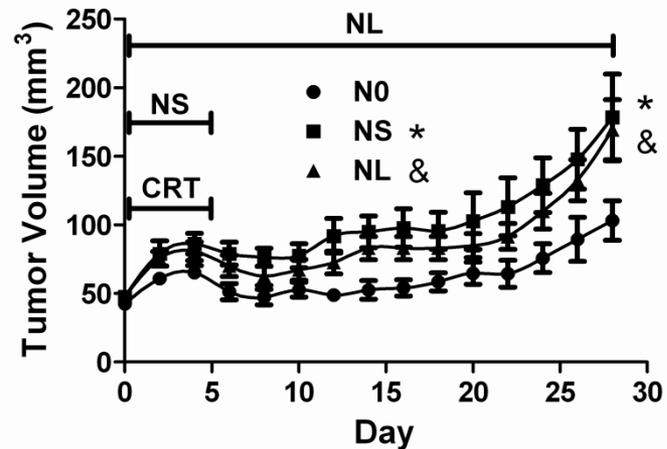
B. Tumor Regrowth with RT and CRT



C. Effect of Nicotine on RT *In Vivo*



D. Effect of Nicotine on CRT *In Vivo*



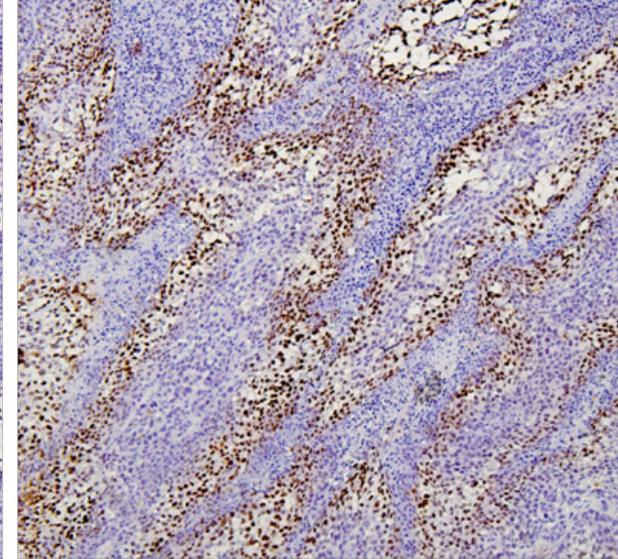
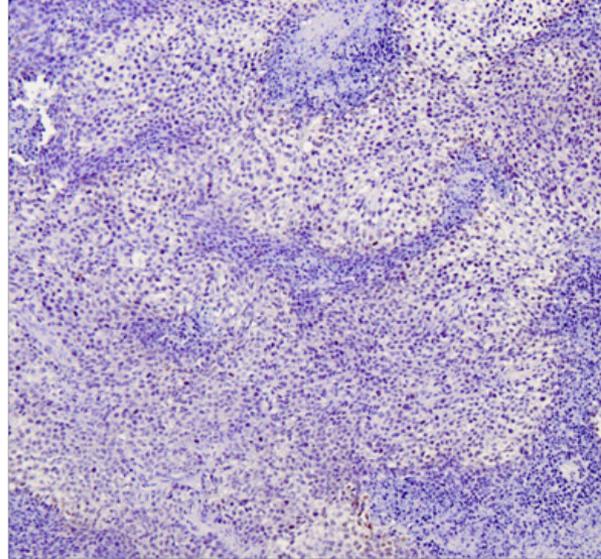
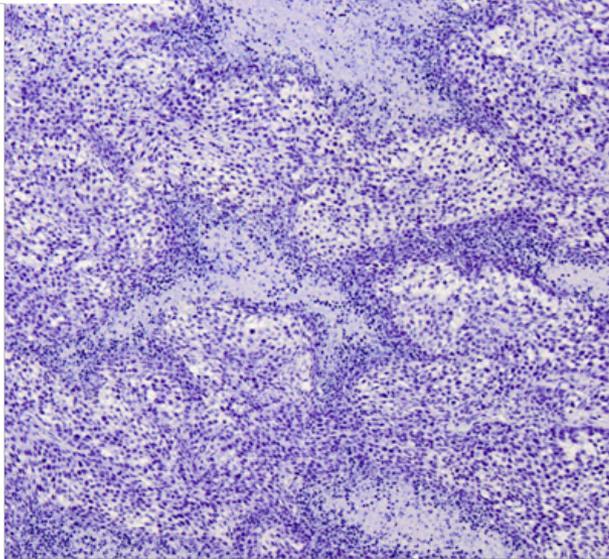
HIF-1 α Expression *In Vivo*

A.

Control (N0)

Short Term Nicotine (NS)

Long Term Nicotine (NL)



B.

Control (N0)

Short Term Nicotine (NS)

Long Term Nicotine (NL)

CA IX

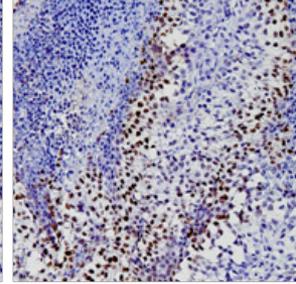
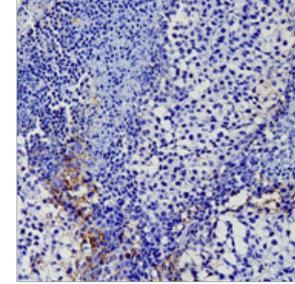
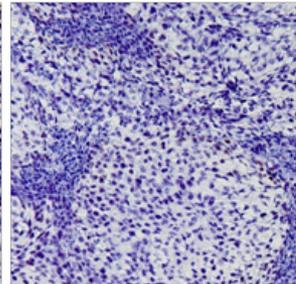
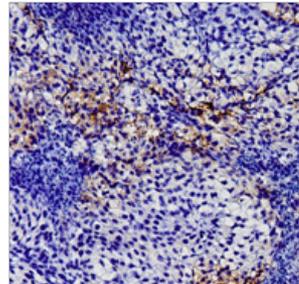
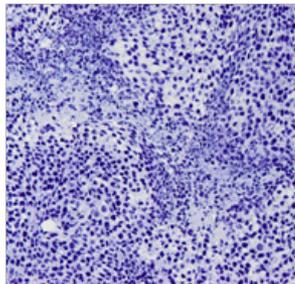
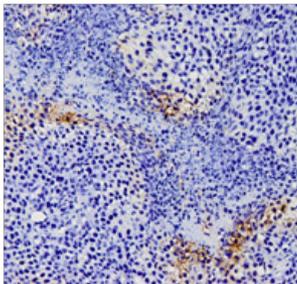
HIF-1 α

CA IX

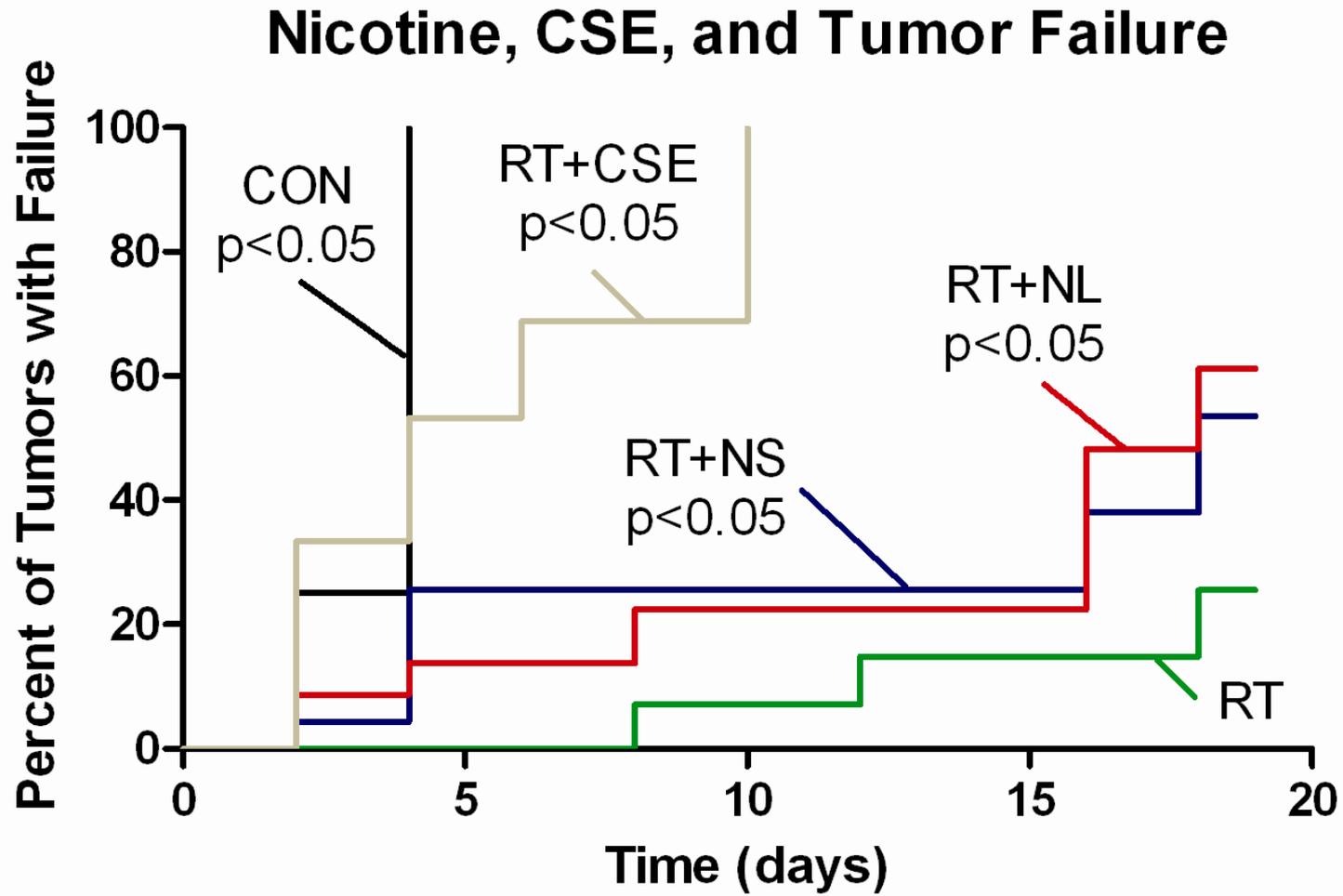
HIF-1 α

CA IX

HIF-1 α

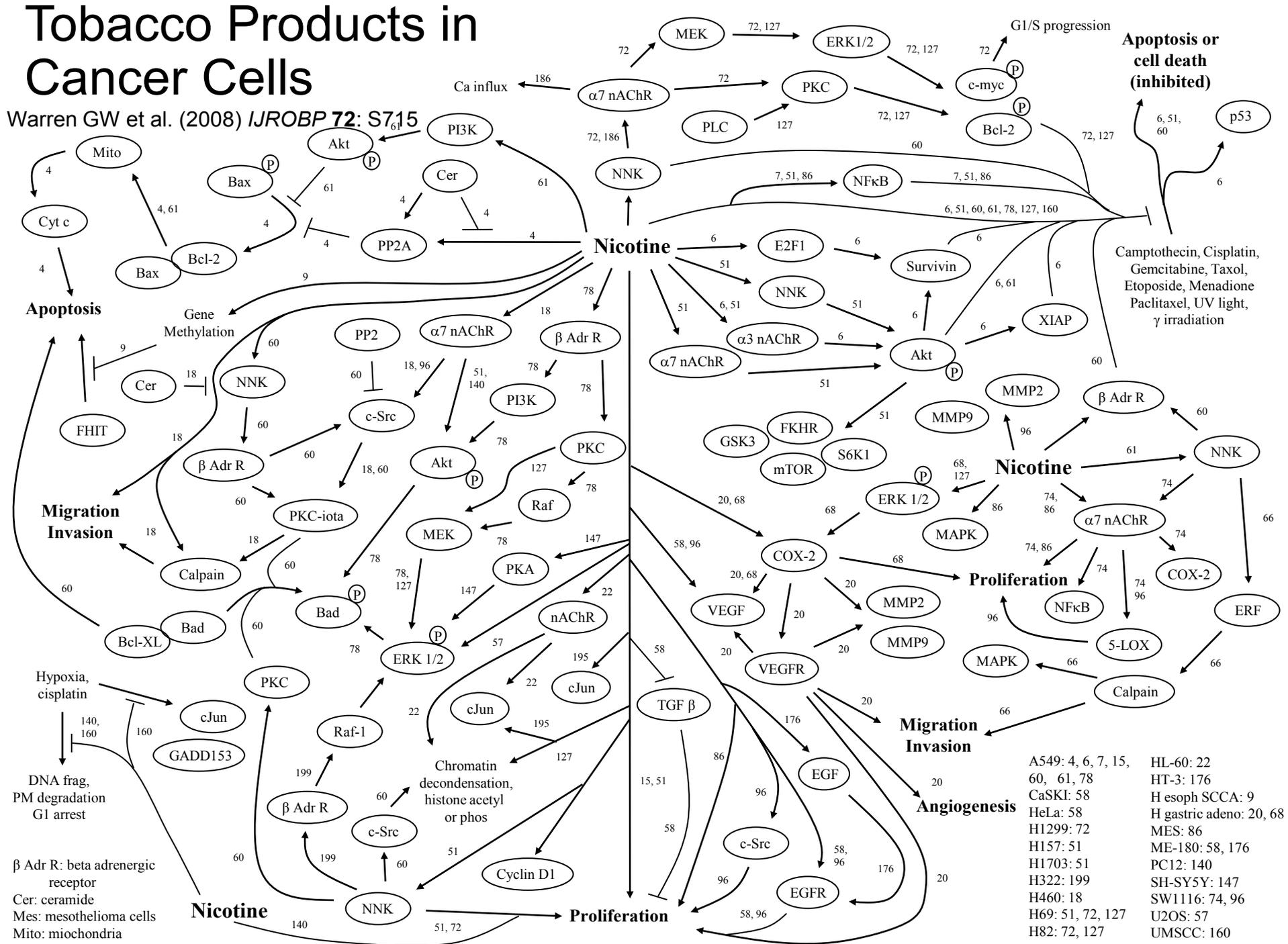


Tobacco, Nicotine, and Tumor Failure

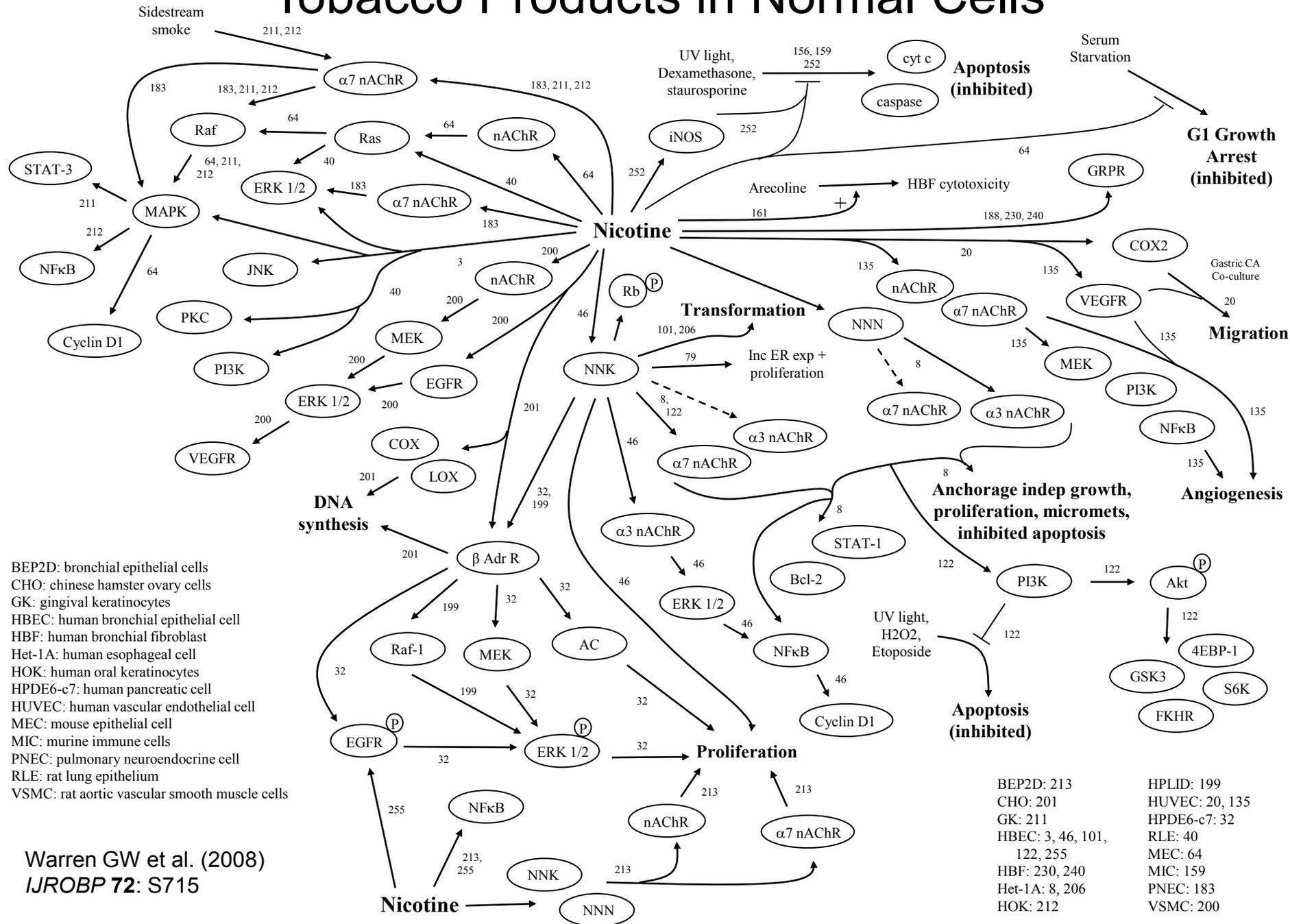


Tobacco Products in Cancer Cells

Warren GW et al. (2008) *IJROBP* 72: S715

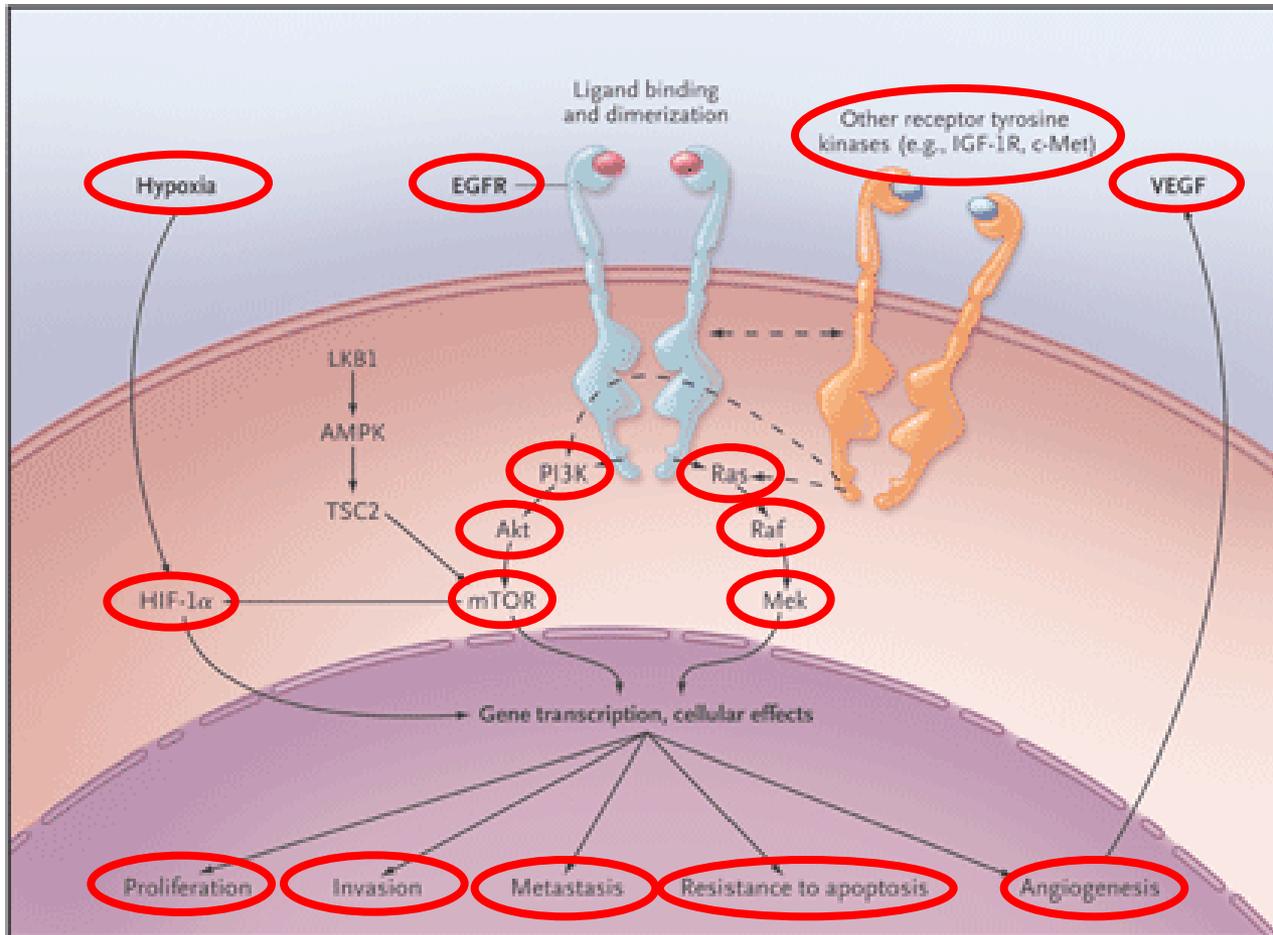


Tobacco Products in Normal Cells



BEP2D: 213
 CHO: 201
 GK: 211
 HBEC: 3, 46, 101, 122, 255
 HBF: 230, 240
 Het-1A: 8, 206
 HOK: 212
 HPLID: 199
 HUVEC: 20, 135
 HPDE6-c7: 32
 RLE: 40
 MEC: 64
 MIC: 159
 PNEC: 183
 VSMC: 200

Targeted Therapy



So...

Tobacco adversely affects cancer treatment
and non-cancer related health outcomes

What can we do about it?

Smoking Cessation and Outcome

Study	Population	Outcome (Smokers)
Chen <i>BJU Int</i> 100:286, 2007	265 NMI bladder CA	Current increase recurrence, recent quitters (<1yr) reverse risk
Barnoya <i>Ca Causes Cont</i> 15:689, 2004	California SEER analysis from 1975-99	Tobacco control programs reduced lung cancer mortality
Aveyard <i>BJU Int</i> 90:228, 2002	Bladder Cancer review	Decreased OS, cessation improve OS
Joshu <i>JNCI</i> 103:835, 2011	1416 prostate, prostatectomy	Cessation by 1 year eliminate increased recurrence by current smoking
Weinmann <i>Ca Caus Cont</i> 21:117, 2010	768 who died of prostate CA (Pros Ca Screening Mort Study)	Most recent smoking status most important predictor for prostate cancer death

Data suggest that cessation may improve outcomes, but...

Tobacco Assessment in Actively Accruing National Cancer Institute Cooperative Group Program Clinical Trials

Erica N. Peters, Essie Torres, Benjamin A. Toll, K. Michael Cummings, Ellen R. Gritz, Andrew Hyland, Roy S. Herbst, James R. Marshall, and Graham W. Warren

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A B S T R A C T

Purpose

Substantial evidence suggests that tobacco use has adverse effects on cancer treatment outcomes; however, routine assessment of tobacco use has not been fully incorporated into standard clinical oncology practice. The purpose of this study was to evaluate tobacco use assessment in patients enrolled onto actively accruing cancer clinical trials.

Methods

Protocols and forms for 155 actively accruing trials in the National Cancer Institute's (NCI's) Clinical Trials Cooperative Group Program were evaluated for tobacco use assessment at enrollment and follow-up by using a structured coding instrument.

Results

Of the 155 clinical trials reviewed, 45 (29%) assessed any form of tobacco use at enrollment, but only 34 (21.9%) assessed current cigarette use. Only seven trials (4.5%) assessed any form of tobacco use during follow-up. Secondhand smoke exposure was captured in 2.6% of trials at enrollment and 0.6% during follow-up. None of the trials assessed nicotine dependence or interest in quitting at any point during enrollment or treatment. Tobacco status assessment was higher in lung/head and neck trials as well as phase III trials, but there was no difference according to year of starting accrual or cooperative group.

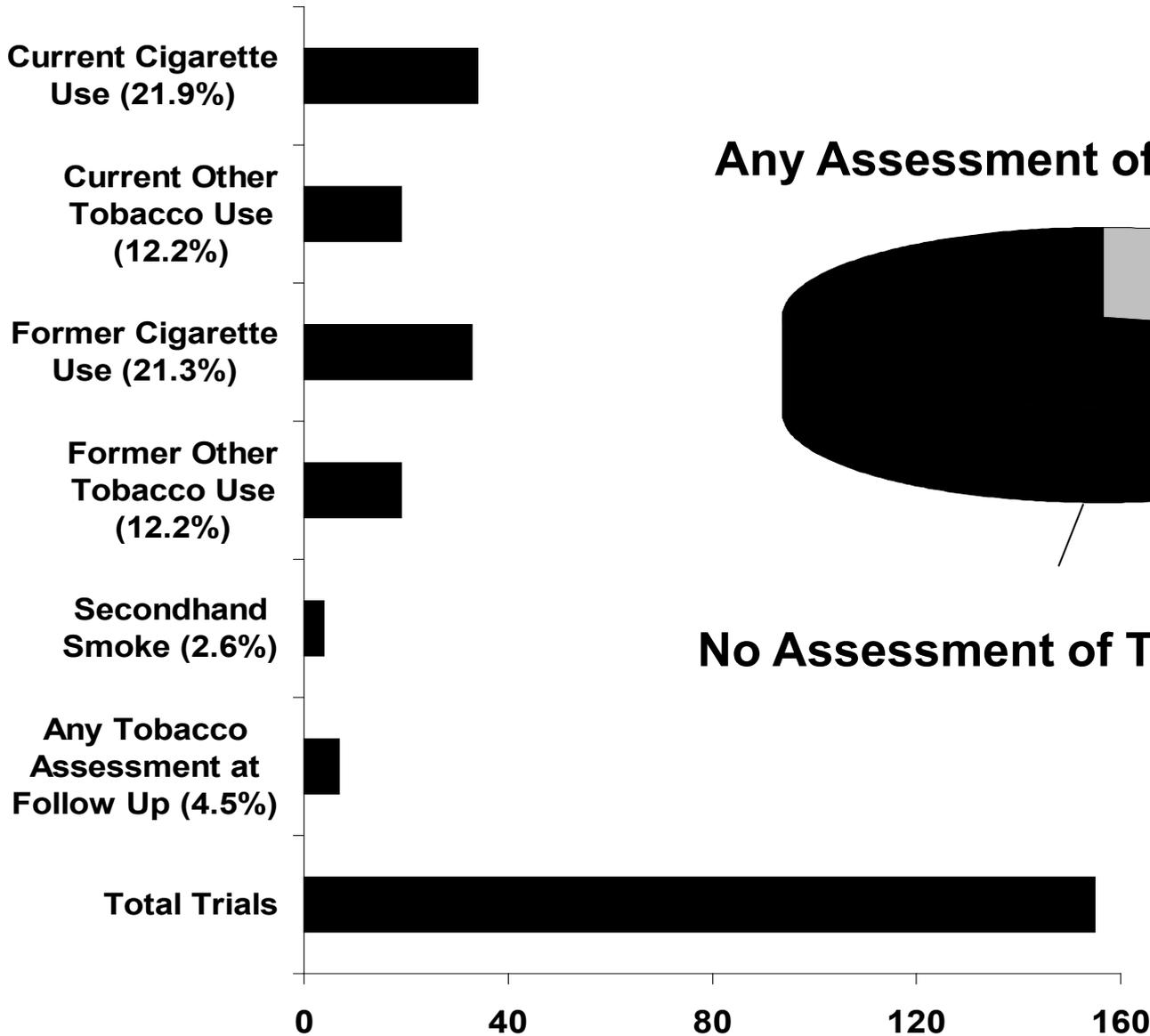
Conclusion

Most actively accruing cooperative group clinical trials do not assess tobacco use, and there is no observable trend in improvement over the past 8 years. Failure to incorporate standardized tobacco assessments into NCI-funded Cooperative Group Clinical Trials will limit the ability to provide evidence-based cessation support and will limit the ability to accurately understand the precise effect of tobacco use on cancer treatment outcomes.

Assessing Tobacco in Cooperative Groups

- 155 Cooperative group clinical trials analyzed for tobacco use
 - 10 cooperative groups
 - Any tobacco use
 - Detailed former tobacco use
 - Detailed current tobacco use
 - Assessments at follow up
 - Cessation assessment/advice/counseling

Assessing Tobacco in Cooperative Groups

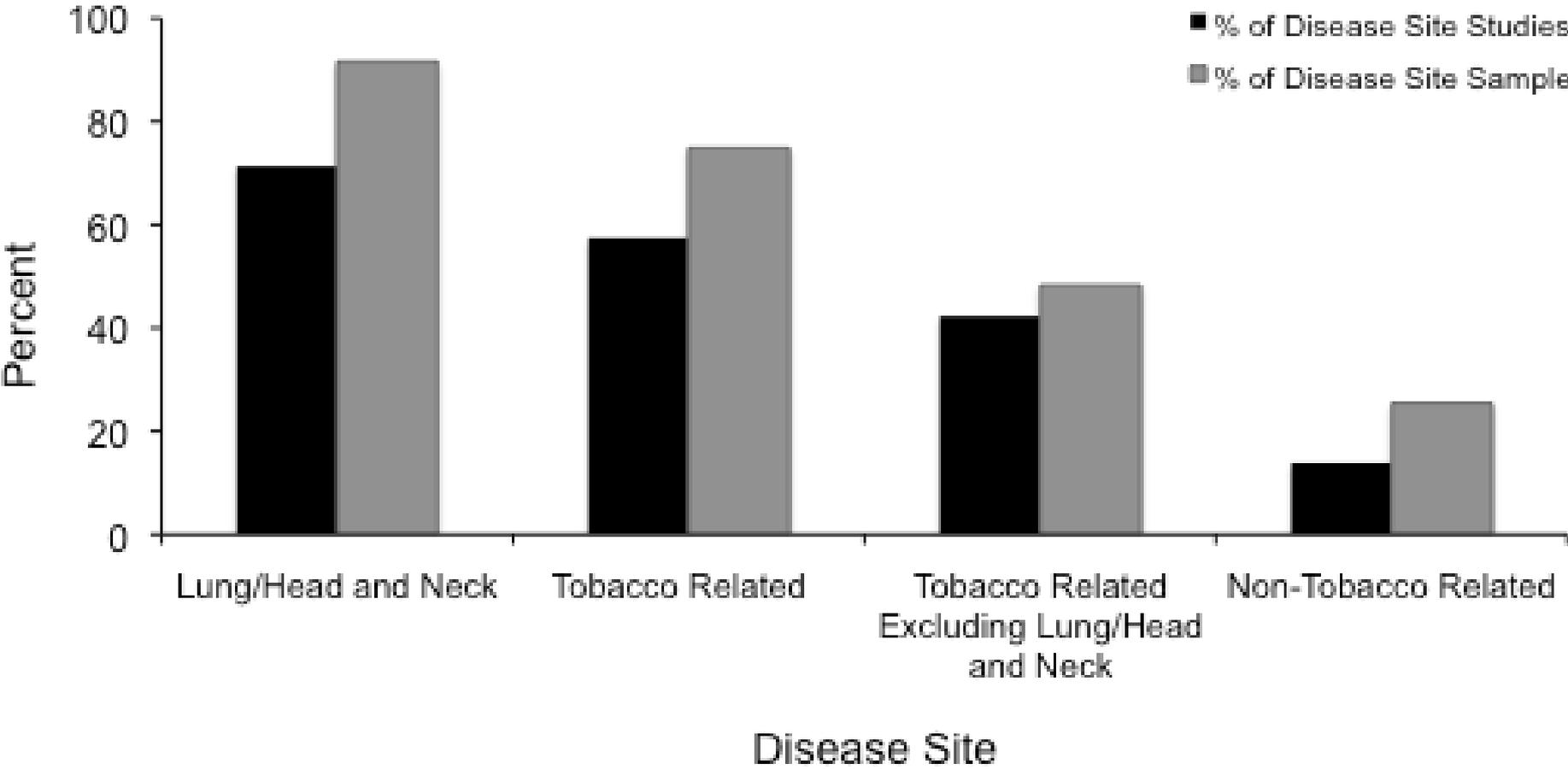


Any Assessment of Tobacco (29%)

No Assessment of Tobacco (71%)

Warren *Proc AACR* abs. 648, 2012
Peters *In Press, J Clin Oncol*, 2012

Assessing Tobacco in Cooperative Groups

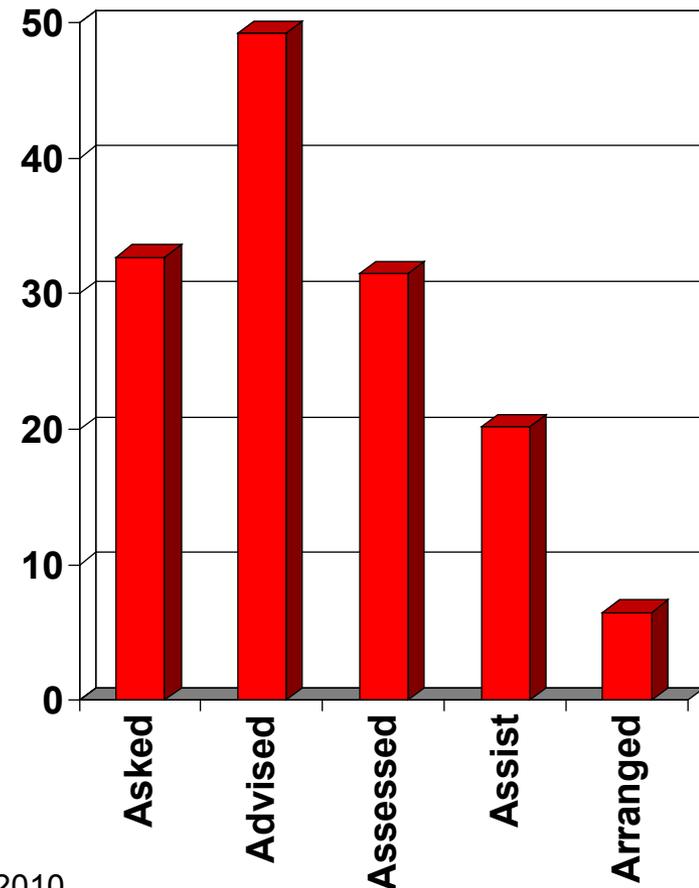


Warren *Proc AACR* abs. 648, 2012
Peters *In Press, J Clin Oncol*, 2012

Cessation Practices in Clinicians?

- Survey in 601 urologists¹
 - 55.6% never discuss cessation
 - 40.7% believe cessation does not affect outcomes
 - 37.7% do not feel qualified to counsel
 - 93.7% have never had cessation training

Survey in 695 patients on exit interview from community physician (percent receiving 5 A's)²



1. Bjurlin *J Urol* 184:1901, 2010

2. Prokhorov *Arch Int Med* 170:1640, 2010

Why? Tobacco in the News

- 5327 stories in the top 50 newspapers¹
 - High propensity for reporting lifestyle (smoking, diet) as related to risk of developing cancer
 - Significant deficit in reporting preventative measures (such as cessation)
- 231 stories in 2003-4 related to breast cancer²
 - Few mention smoking cessation

1. Jensen *J Health Commun* 15:136, 2010\

2. Atkin *J Health Commun* 13:3, 2008

Smoking Rates in Cancer Survivors?

- Survey of 2027 cancer patients in NCI Health Information National Trends Survey¹
 - Claim decreased smoking rate in cancer survivors
- NHANES data in 2188 cancer survivors²
 - Claim lower current smoking rates
 - Analyze according to gender, SES, age, etc.
- 1600 cancer survivors in annual National Health Interview Survey (2000)³

No mention of potential bias due to increased mortality in smokers

1. Mayer *Nicotine Tob Res* 13:34, 2011
2. Tseng *J Cancer Surv* 4:313, 2010
3. Sabatino *J Clin Oncol* 25:2100, 2007

Cancer Survivorship

- Increased survivorship in cancer patients warrants preventative efforts¹
 - Increased continuing medical care
 - Smoking cessation emphasized

... but ...

- Review of lifestyle changes in breast cancer²
 - Recommend diet, activity, and weight loss changes
 - No recommendations for smoking cessation

1. Frieden *MMWR Morb Mortal Wkly Rep* 60:269, 2011

2. Kellen *Breast Cancer Res Treat* 114:13, 2009

Tobacco and Personalized Medicine

- Tobacco use assessments should
 - Increase the accuracy of analyzing clinical outcomes
 - Increase the efficacy of cancer treatment
 - Identify molecular signatures associated with disease progression and therapeutic resistance
 - Increase the synergy between cancer treatment and evidence based non-cancer medicine
- Tobacco is a potentially unique model of cancer biology that can be used to evaluate therapeutic resistance

Cancer Policy Considerations

- **Mandatory tobacco assessment and cessation referral as a clinical STANDARD OF CARE**
 - Standardized evidence based assessments
 - Longitudinal assessments at diagnosis and during follow-up
- Include tobacco assessments in clinical trials
 - Develop standard recommendations for assessment parameters/tobacco data to be collected in trials

Cancer Policy Considerations

- Currently, no generally accepted method for assessment advocated by any national organization for cancer patients
 - Leadership by NCI?
 - Shared participation by vested parties
- Realize cancer patients are inherently different than non-cancer patients
 - Captive audience during/following treatment
 - Immediate quit more relevant than general patient
- Use media to assist in message delivery

Tobacco: The Great Continuum

- In cancer patients, tobacco:
 - Decreases therapeutic response
 - Increases recurrence
 - Increases toxicity
 - Decreases quality of life
 - Decreases survival
- However, in all patients, tobacco:
 - Increases cardiopulmonary risk
 - Increases cerebrovascular risk
 - Increases risk of malignancy (or second malignancy)

Summary for Tobacco

**Tobacco use is bad.
(even in cancer patients)**