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Amanda McCarthy Date

Lack of ecological association between state-level cervical and colorectal cancer incidence and nitrosamine exposure from condom use for a cross-sectional study of the United States

By

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Master of Public Health

Global Epidemiology

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Bachelor of Arts, Vassar College, 2013

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An abstract of

A thesis submitted to the Faculty of the

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Abstract

Lack of ecological association between state-level cervical and colorectal cancer incidence and nitrosamine exposure from condom use for a cross-sectional study of the United States

By Amanda McCarthy

Background: N-nitrosamines are a class of carcinogenic compounds that are commonly found in a wide variety of sources, including tobacco products, cured or fermented foods, and rubber goods, such as latex gloves. Nitrosamines are also found in condoms and no previous research has explored whether condom use is associated with cancer incidence.

Methods: Using state-level data from 2012, potential ecological association between colorectal and cervical cancer incidence and condom use was studied with multiple linear regression models, controlling for potential confounders.

Results: No ecological association between reported condom use and cervical or colorectal cancer was found in either bivariate or multivariable analyses, controlling for variables including race/ethnicity, smoking, obesity, physical activity and fruit/vegetable consumption.

Conclusions: This study finds no evidence indicating an association between nitrosamine exposure from condoms and incidence of cervical and colorectal cancer. Condoms provide substantial and measurable public health benefits, and providers and healthcare organizations should continue to recommend and promote them without hesitation.

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Finally, all my love and gratitude to my friends and family. To my Rollins friends, I could not have done it without you all—we're (almost) done! To everyone else, I'll stop talking about this and return calls/emails in a timely manner now, I swear.

Contents

Introduction

Condoms are one of the most important public health tools in sexual health, playing roles in human immunodeficiency virus (HIV) prevention, prevention of sexually transmitted infections (STIs), and family planning. There has been substantial investment by local governments, international health agencies and non-governmental organizations (NGOs) to increase supply and uptake of condoms (Fisher et al., 2016; Johnson et al., 2008; Pienaar et al., 2016; Huang et al., 2015). Increasing access to condoms and education about STI and HIV prevention has resulted in important gains in condom use, especially among high-risk populations like commercial sex workers (CSW) and men who have sex with men (MSM) (Johnson et al., 2008; Milrod & Monto, 2016; Bandewar et al., 2016; Subramanian et al., 2013). However, condom usage among CSWs continues to face barriers including client preference for unprotected sex, inconsistent condom supply, and policies that criminalize sex work (Bandewar et al., 2016; Jung, 2013). Among MSM populations, condom use is mediated by perceptions of risk and condom self-efficacy (Milrod & Monto, 2016; Ramanathan et al., 2016; Jung, 2013). National rates of condom use in the US vary by race, age, gender, and sex act: 24.7% of men and 21.8% of women report condom use at last vaginal intercourse while 26.5% of insertive male partners, 44.1% of receptive male partners and 10.8% of receptive female partners report condom use at last anal intercourse (Reece et al., 2010). One of the barriers to condom usage in low-income countries is negative perception or rumors about

condoms (Thomsen et al., 2004); a study in Tanzania found that negative beliefs about condoms were significant predictors of willingness to use condoms (Siegler et al., 2012). Perceptions by the public about condom safety and efficacy directly affect their use and thus can adversely affect sexual and reproductive health programs (Davis et al., 2014; Siegler et al., 2012).

Negative beliefs about condoms include the belief that condoms cause cancer (Siegler et al., 2012). This is actually a concern among some condom manufacturers —specifically, the release of nitrosamines from condoms (ISO/TC 157, 2015). Nitrosamines are a class of carcinogenic compounds that can be produced in the manufacturing process of rubber products. Formed by the reaction of nitrites with secondary or tertiary amines, nitrosamines can vary in their carcinogenicity, with two potent carcinogens, N-nitrosodiethylamine (NDEA) and N-nitrosodimethylamine (NDMA), often used as indicators of nitrosamine presence (Selin, 2011). The World Health Organization (WHO), the European Union, and the US Environmental Protection Agency (EPA) classify NDEA and NDMA as probable or presumed human carcinogens (Selin, 2011).

The US Department of Health and Human Services released the *13th Report on Carcinogens* in 2014, which included 15 listings of nitrosamines classified as "*known or reasonably anticipated*" carcinogens (NTP, 2014). Nitrosamines are linked with the development of multiple different types of cancer in many different animal

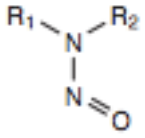
models, including colon tumors in male rats, female mice and guinea pigs, as well as cervical tumors in female shrews following rectal or oral administration (NTP, 2014).

Nitrosamines have been found in food, cosmetics, tobacco products, and rubber goods such as balloons, pacifiers, baby bottle teats, and also condoms (NTP, 2007; Dong et al., 2015; Altkofer et al., 2005; Fritschi et al., 2015; Nawrocki & Andrzejewski, 2011). Nitrosamine-related cancer studies in humans are relatively scarce, though they include epidemiological studies of cancer mortality for occupational cohorts, as well as case-control or ecological studies conducted on dietary exposure (Monarca et al., 2001; de Vocht et al., 2007; NTP, 2014). Subsequent sections will discuss studies and regulations regarding nitrosamine exposure in occupational settings, food and drinking water, as well as rubber products like pacifiers, rubber gloves, and condoms[1]. The migration of nitrosamines from condoms to mucous membranes like the vagina and rectum, which have higher absorption, is a possible risk (Eisenbrand, 2005).

[1] For conversion between exposure units:
1 µg /L = 1000 µg /m^3
1 µg /L = 1 part per billion (ppb)
1 µg/kg =1 ppb

The carcinogenic qualities of nitrosamines have been demonstrated in animal models and migration of nitrosamines from condoms were simulated in artificial conditions(NTP, 2014; Biaudet et al., 1997; Altkofer et al., 2005), yet nitrosamines are also commonly found in a large variety of settings, including natural occurrence in some fruit and vegetables. Little research has established whether current levels of exposure to nitrosamines, such as through condoms, are associated with cancer incidence. It is important to better characterize this relationship not only to investigate a possible safety concern related to current condom manufacturing methods, but also to allow for condom rumors to either be supported or refuted with evidence.

To address the dearth of population-based studies of nitrosamine exposure from condoms and cancer incidence in the literature, this paper provides an ecological analysis, using cross-sectional data from the United States. Regressions were conducted, assessing associations between reported condom use and incidence rate of cervical and colorectal cancers by state. Additional demographic and health behavior predictors were included as control variables in multiple linear regression.



Generic *N*-nitrosamine structure (NTP, 2014)

Nitrosamines in food and water

Nitrosamines have been found in drinking water as a result of the disinfecting process (Nawrocki & Andrzejewski, 2011). In 2004, the EPA published Method 521, which laid out the methodology for nitrosamine detection in drinking water (Selin, 2011). The second Unregulated Contaminant Monitoring Rule (UCMR) monitored six types of nitrosamines in drinking water systems in the United States (Selin, 2011); however, the third UCMR omitted nitrosamines from the screening survey and is monitoring different types of disinfectant residual compounds (EPA, 2012).

Through the Clean Water Act, EPA also released water quality criteria which limit NDMA levels to 0.00069 µg /L in water, among other nitrosamine guidelines, although these are non-regulatory and based on assessment of 10^{-6} carcinogenic risk level, which defines the acceptable level of risk as one additional cancer case from one million people (Selin 2011). Some states have also instituted monitoring and notification guidelines for nitrosamines in drinking water, including a guideline of 0.01 µg/L of NDMA in drinking water in Massachusetts and a notification level of 0.01 µg/L for NDEA, NDMA, and N-Nitrosodi-n-propylamine (NDPA) in California (Mass. DEP, 2004; California DPH, 2011). However, the methodology used to detect nitrosamines in food or rubber products cannot be utilized in water testing because secondary amines (a proxy for detection after derivatization) are far more abundant in water and would thus greatly overestimate nitrosamine presence (Nawrocki & Andrzejewski, 2011).

Nitrates and nitrites are naturally occurring in some foods, including vegetables (Bryan, 2012). Nitrate fertilizers may contaminate agricultural products, or nitrites may be added as a preservative and to prevent *Clostridium botulinum* growth (Bryan et al., 2012; Park et al., 2015). Human stomachs have sufficiently low pH (3-4) to facilitate the synthesis of nitrates or nitrites with secondary amines to create nitrosamines through N-nitrosation (Bryan et al., 2012). Soil microorganisms may also facilitate nitrosation in agricultural products, and nitrosamines may also be formed during fermentation (Park et al., 2015). NDMA concentrations in beer were formally high, due to nitrosation of malts during brewing, although there has been significant reduction in NDMA in alcoholic beverages due to greater attention to nitrosamines and changes in brewing processes (Bryan et al., 2012).

A study of 387 foods common in the Korean diet were analyzed with tandem mass spectrometry for seven types of nitrosamines; agricultural foods contained between 0.13 to 6.1 μg/kg of detectable NDMA, compared to 0.31 to1.54 μg/kg in processed meat (Park et al., 2015). Seasonings contained the highest concentration of NDMA: 13.48μg/kg (Park et al., 2015). Another study using a similar methodology found a general increase in nitrosamine storage after a week of storage at 4°C, with the highest nitrosamine concentration of 1.75 to 34.75 μg/kg of N-nitrosodipropylamine and 1.50 to 4.26 μg/kg of N-nitrosopiperidine found in processed meats (Scheeren et al., 2015). These constitute minute amounts of nitrosamine, especially compared to regulatory standards; in Denmark, the

maximum amount of added sodium nitrate for meat products is 60000 μg/kg, which is lower than the threshold of 150,000 μg/kg in other EU states (Herrmann et al., 2014).

Improvements in technology and methods of detection have increased the accuracy of nitrosamine detection in foods. Using solid supported liquid extraction or liquid-liquid extraction to analyze food items may limit heat-facilitated nitrosation during testing, compared to the older method of distillation (Park et al., 2015; Scheeren et al., 2015). On the other hand, mass spectrometry increases sensitivity of nitrosamine detection and quantification, as well as increased ease of simultaneous testing for a wide variety of nitrosamines (Hermann et al., 2014; Park et al., 2015). Improvements in detection may not necessarily correspond to increases in risk or exposure, while changes to food or alcohol production may be in reaction to public controversy rather than conclusive scientific evidence or consensus.

The potential risk of dietary nitrosamine exposure must be weighed against the potential benefits of pesticides to improve crop yield, drinking water disinfection, and botulism prevention. In addition, nitrates and nitrites can also form nitric oxide (NO), which plays important roles in cell signal transduction and is the subject of intense scientific scrutiny in lowering blood pressure and improving cardiovascular health (Bryan et al., 2012; Butler, 2015). Since endogenous nitrosation also happens

as S-nitrosation, which favor NO production, dietary sources of nitrates or nitrites cannot be dismissed wholesale as unfavorable (Bryan et al., 2012).

Early population-based toxicological assessments of endogenous nitrosation of dietary nitrate or nitrite suggested association with hepatotoxicity and possible carcinogenicity (Lijinsky, 1999). However, data from recent case-control and cohort studies have yielded different results for different types of cancer. Several large, recent prospective cohorts concluded that there was no association between dietary nitrate or nitrite intake and gastric cancer incidence (Bryan et al., 2012, Butler, 2015). A European prospective cohort was formed to study the association between gastric cancer and N-nitrosation products, specifically NDMA: there were 514 incident cases over the course of 6 years in a sample of 500,000 people but ultimately null association (HR = 1.00, 95% CI: 0.7, 1.43) (Jakszyn, 2006, cited in: Bryan et al, 2012). The Netherlands Cohort study followed 120,852 people for 16 years to investigate association between dietary NDMA or nitrite consumption and esophageal and gastric cancer subtypes (Keszei et al., 2013). There were some slight positive associations which were only significant among men: the most significant findings were for esophageal squamous cell carcinoma and NDMA intake (an increase in 0.1 –μg of NDMA /day corresponded to HR: 1.15; 95% CI: 1.05, 1.25) and nitrite intake (an increase of 100 –μg of nitrite /day corresponded to HR: 1.19; 95% CI: 1.05, 1.36) (Keszei et al., 2013). A Canadian case-control study found a significant increasing trend of colorectal cancer risk as quintiles of NDMA intake increased,

while the odds ratio for colorectal cancer was 1.42 (95% CI: 1.03, 1.96) when comparing the highest to the lowest quintile (Zhu et al., 2014).

It is important to note that estimation of nitrate and nitrite intake for these studies tends to come from food diaries, which have issues of recall bias. Additionally, these serve as proxies for NDMA nitrosation, which are estimated based on published values for certain foods, can vary from the actual composition, and do not take into consideration understudied dietary sources like seasonings (Butler, 2015; Keszei et al., 2013; Park et al., 2015). Because so much of the literature for dietary nitrosamine exposure is focused on the endogenous processes, there are fewer correlates for potential nitrosamine exposure from condom use when it comes to testing methodologies and cancer sites that are most likely affected. Exposure through food is dependent on diet type and involves varying amounts ingested potentially every day, rather than selective and time-bound exposure through condoms.

Occupational exposure to nitrosamines

Occupational airborne nitrosamine exposure and associations with cancer have primarily been studied among current or former employees of rubber manufacturing plants and workplaces with pesticide use. Though it is well established that workers in rubber manufacturing plants have historically elevated rates of cancer, the variety of carcinogens they are exposed to in addition to

nitrosamines, including aromatic amines and polycyclic aromatic hydrocarbons, obfuscates causal relationships (Bolognesi & Moretto, 2014). Sampling of airborne particulates in 4 Italian rubber manufacturing factories for 8 hours on two non-consecutive days by Monarca, et al. revealed concentrations of 100–980 μg/m^3 of NDMA and 770–2280 μg/m^3 of N-nitroso-morpholine (NMOR) through gas chromatography (2001).

A cohort study of Germans who worked in rubber factories from the 1950s onward showed significant increased mortality for esophageal cancer (RR 7.3, 95% CI: 1.9, 27.8) and oral-pharynx cancer (RR 3.9, 95% CI: 1.4, 11.1) when comparing high (>15 μg airborne nitrosamine/m^3) to low (<2.5 μg airborne nitrosamine /m^3) nitrosamine exposure (Straif et al., 2000). There was no significant association between increased nitrosamine exposure with prostate, lung, or stomach cancer. There were relatively few cancer-related deaths, which resulted in wide and imprecise confidence intervals for these rate ratios; a further limitation of this study was that measurement of the nitrosamine exposure was conducted in the 1980s, which may not have captured the true exposure levels (Straif et al., 2000). This is particularly relevant as nitrosamine exposures have increased and decreased in rubber manufacturers of different European countries, with some countries like Germany instituting an exposure limit of 2.5 μg/m^3 for total nitrosamines (de Vocht et al., 2007; Straif et al., 2000).

Epidemiological studies have attempted to characterize the potential risk of

elevated cancer mortality or incidence based on years of working in rubber manufacturing industries while controlling for smoking as a potential confounder. In Australia, a population-based case-control study where exposure was assessed based on reported work experience in rubber manufacturing, metal working or workplaces with high pesticide use found no significant association between risk of pancreatic cancer and occupational exposure to N-nitrosamines, controlling for smoking (Fritschi et al., 2015) In Shanghai, China, a case-cohort study found an increasing trend in lung cancer mortality with increasing number of years of employment in the tire-curing industry, after controlling for economic status and smoking (Li & Yu, 2002). However, the lung cancer mortality rate ratio was only significant (3.76; 95% CI: 1.44, 9.86) within the group that had 30-45 exposure-years in the curing department, which not only covers a long period of exposure but may also encompass potential changes in manufacturing processes as well as represent a sub-population that is older and thus more likely to die of cancer.

Bolognesi, et al. evaluated the strength of evidence regarding genotoxic risks of occupational exposures, as a possible mechanism for elevated cancer rates among rubber manufacturing workers (2011). Reduction in telomere length, chromosome aberrations, and sister chromosome exchange (SCE) are biomarkers for potential chromosome damage in genotoxic risk assessments. Two case-control studies of Polish tire manufacturing workers who were exposed to nitrosamines and other carcinogens between 0.5 to 35 years found increased chromosomal aberrations and

SCE among cases, though results where borderline (Sasiadek, 1992, 1993, cited in: Bolognesi et al., 2014). Li, et al. found significant association between airborne nitrosamine exposure and reduced telomere length among 157 Swedish workers (2011, cited in: Bolognesi et al., 2014). Measured nitrosamine levels in the air were between 70 and 35,500 $\mu g/m^3$, which is a wide range of exposure. In addition to the wide range of dose exposure in both these studies, the high individual variability and confounding by individual genetics, age, and lifestyles (smoking, diet, etc.) limits causal interpretations. Furthermore, the variety of processes and complex chemical milieu of rubber manufacturing industries limit industry-wide generalizations and complicates causal associations, while technological advances and more stringent safety measures may also mitigate risk and limit comparisons of studies from different time periods (de Vocht et al., 2007).

While there are a number of epidemiological studies examining occupational exposure to nitrosamine and increased cancer incidence or mortality, associations with different cancers and the dose-response relationship remain inconclusive; there are also environmental and individual confounders and systematic biases which are not accounted for, including the healthy worker effect. Occupational exposure to nitrosamines is fundamentally different compared to condom-associated nitrosamines, as workers are primarily breathing in airborne nitrosamine particulates, which affect the respiratory system rather then vaginal or anal mucosa. In addition to potential differences in absorption of nitrosamines

through different mucosa, the length of a daily workplace exposure (potentially over years of employment) is also vastly different than condom-associated exposure during sex. Finally, levels of airborne nitrosamines associated with elevated carcinogenic or genotoxic risks may not correspond to similar levels of elevated risks for nitrosamine migration from condoms.

Nitrosamines in rubber products

A number of researchers reported on migration of volatile nitrosamines from baby bottle teats and pacifiers in the 1980s and 1990s; one estimate of average daily exposure was less than 0.05 µg/kg body weight for adults, but children and toddlers were considered at greater risk, due to increased susceptibility and their exposure to rubber teats and pacifiers (Proksch, 2001). Migration limits for rubber products that are in contact with food or beverages are determined based on contact area, temperature of the object at time of contact, length of contact and frequency of contact. The Consumer Product Safety Commission instituted a voluntary maximum standard of 10 parts per billion (ppb) of any single nitrosamine or 20 ppb of combined nitrosamines for rubber pacifiers, and the Food and Drug Administration set an action level of 10 ppb for rubber baby-bottle nipples (NTP, 2014). The EU Commission Directive 93/11/EEC set a maximum migration of 10 µg/kg of nitrosamines and 100 µg /kg for nitrosatable substances in rubber products like teats and pacifiers (cited in: Feng et al., 2010). The European Committee for Standardization specified the EN12868 method for nitrosamine and nitrosatable

compound extraction from baby bottles and rubber nipples, using artificial saliva and a contact period of 24 hours at 40°C (Feng et al., 2010). A standardized method to test nitrosamine migration through artificial saliva allows for reproducibility (rather than reliance on scarce human or animal physiological samples) and allows for comparability across countries and samples. However, applicability to condoms may be questionable, given the differences in exposure time (sucking on a pacifier for hours every day compared to sexual activity for minutes) as well as the differences in permeability and absorption through oral or ano-genital membranes.

Biaudet et al. detected the migration of nitrosamines from 7 brands of condoms (removed of their lubricant) into artificial saliva, which was prepared in concordance with EN12868, as well as migration in diluted cow secretion, she-goat secretion and human cervical mucus (1997). Migration testing took place at 40°C, and the sealed sample was stirred for 24 hours (Biaudet et al., 1997). Migration of nitrosamines and nitrosatable compounds was much lower in physiological secretions (mostly non-detectable) compared to artificial saliva, possibly due to differences in viscosity (Biaudet et al., 1997). Because of the difficulty in obtaining women's cervical mucus the sample size was extremely limited, with only 3 of the 7 condom brands tested in physiological secretions (Biaudet et al., 1997).

Artificial sweat tests conducted with 32 rubber condoms available from German stores found nitrosamine migration of less than 10 μg/kg to 660 μg/kg of material in condoms (Altkofer et al., 2005). Nitrosamine migration was conducted in an

artificial sweat solution (a 1 L aqueous solution of "4.5 g NaCl, 0.3 g KCl, 0.3 g Na_2SO_4, 0.4 g NH_4Cl, 3.0 g lactic acid, and 0.2 g urea") which was applied both inside and outside the condom (Altkofer et al., 2005). The condom was then sealed and subjected to a dynamic migration test or shaking water bath for 1 hour at 37 °C; the sweat solutions with migrates were then analyzed with gas chromatography and thermal energy analyzer (Altkofer et al., 2005). The researchers acknowledged that the length of contact in their experiments would not necessarily reflect the length of condom use in a sexual encounter; they replicated the migration and testing method for one type of condom but reduced the time in the water bath to ten minutes. For this condom type, levels of nitrosamine migration were similar, with 263 μg/kg released in an hour-long migration test, compared to 260 μg/kg in ten minutes (Altkofer et al., 2005). While this suggests that migration of nitrosamines from condoms may occur in a relatively short time period, further study with a larger sample size would be necessary to generalize, as the next study attempted to do.

Using gas chromatography with thermal energy analyzer, Feng et al. tested nitrosamine migration among 37 condom brands available from Chinese stores, using both an artificial sweat and artificial saliva test (2010). Their artificial sweat tests utilized the same formula as Altkofer, et al. (2005), but also lowered the pH to 4.5 to simulate the vaginal environment and reduced the contact time to 10 minutes (Feng et al., 2010). Like Altkofer, et al., there was interest in studying the effect of contact time on migration, so one condom brand was subjected to 5, 10, 20, 30, 60, and 120 minutes of migration time, with three samples for each time frame (Feng et

al., 2010). The artificial saliva test was conducted according to method EN12868, with the same artificial saliva solution and migration period of 24 hours at 40°C, though condoms were not boiled before testing (Feng et al., 2010). Their sweat test results showed 17 brands types released 15.6 - 792.9 µg/kg of nitrosamines and 26.29 - 1959.69 µg/kg of nitrosatable substances, while their saliva tests found that all 37 condoms released 5.25-1289.76 µg/kg of nitrosamines and 63.57-4705.53 µg/kg of nitrosatable substances (Feng et al., 2010).

Feng, et al. discussed potential shortcomings of their saliva test, citing contact times that were too long compared to condom use during sexual encounters as well as the presence of $NaNO_2$ in the artificial saliva solution, which can undergo nitrosation and thus inflate estimates (Feng et al., 2010). Alternatively, the sweat test may underestimate vaginal nitrosamine migration because it does not contain this ingredient, given the spontaneous nitrosation that can occur in the vagina (Proksch, 2001; Biaudet et al., 1997). With the stepwise contact time methodology, they corroborated the idea that migration of nitrosamines in condoms happens primarily within the first 10 minutes (Fend et al., 2010). While the changes to methodology more closely approximate vaginal exposure, applicability to anal exposure is still in question.

In the aforementioned migration tests with condoms, the sweat solution was based on the German standard used in testing colorfastness of plastic toys (Altkofer et al., 2005), which does not adequately reflect the vaginal and anal environment.

Absorption through the vaginal or anal tissues was also not considered as a potential mediator, though testing absorption or permeability would be rather difficult, as in-vivo testing would be unethical and not feasible. In-vitro testing of delivery for topical drugs intended for vaginas may utilize porcine vaginal tissues as models to test permeability (Li et al. 2012). While porcine tissues are good in-vitro models, sharing similar tissue histology and lipid compositions, permeability is not exactly identical for all types of permeants (van Eyck & van der Bijl, 2005). Additional physiological factors to consider include cyclical changes in cervical mucus and epithelial thickness, vaginal fluid volume and composition, as well as flora in the vagina (Srikrishna & Cardozo, 2013). Recent studies on the development of HIV-preventive microbicides have yielded more information on the rectal environment: rectal mucosa, unlike vaginal mucosa, is slightly alkaline (pH: 7-8) and consists of water, mucins and small amounts of antimicrobial factors (Nunes et al., 2014). Rectal mucus also has microbiota and associated enzymes, which are being studied in the context of pathogen defense; this may be an additional factor to study in the metabolism or absorption of condom-associated nitrosamines (Nunes et al., 2014).

Overall, the levels of exposure to nitrosamines from condoms are much lower than other potential sources. With the condom brand that released the highest amount of nitrosamines (792.89 μg/kg), Feng, et al. estimated a nitrosamine exposure level of 1.2 μg for each ten-minute sexual encounter or lifetime exposure of 1.8 mg (assuming 50 condoms used for at least 10 minutes/year for 30 years) compared to

an estimated daily exposure of 0.2–0.5 mg from food (Feng et al., 2010; Proksch, 2001).

Colorectal cancer

In the United States, colorectal cancer is the second leading cause of cancer death and the third most common type of cancer. Colon cancer comprises about three quarters of colorectal cancer and less is generally known about rectal cancer (Giovannucci, 2002). Colorectal cancer is positively associated with diet, including high fat, red meat, and alcohol consumption. High body mass index (BMI) and smoking are also risk factors for colorectal cancer (Roncucci & Mariani, 2015; Potter, 1999; Wong, 2008). Consumption of vegetables, physical activity, postmenopausal hormones, and regular non-steroidal anti-inflammatory drug (NSAIDs) use are inversely associated with colorectal cancer ((Danaei, 2005; Roncucci, 2015; Potter, 1999; Wong et al., 2008). Colorectal cancer rates are higher among men compared to women, and appear to be more common among certain ethnicities, including African-Americans, Native Americans, and certain Asian American ethnicities (Wong et al., 2008; USPSTF, 2008).

Patients 50 years or older make up more than 80% of diagnosed colorectal cancer cases (USPSTF, 2008). Screening is an important preventative measure, particularly as the cancer progresses in a stepwise fashion and often develops from precancerous polyps. The US Preventive Services Task Force (USPSTF) recommends regular screening for colorectal cancer beginning at age 50 and continuing until 75

years old. Individuals with a family history of colorectal polyps or colorectal cancer, inflammatory bowel disease, Crohn's disease, ulcerative colitis, or genetic syndromes like Lynch Syndrome, or a familial adenomatous polyposis (FAP), may need to be tested before age 50. For most individuals age 76 to 85 years, USPSTF does not recommend routine screening and for most individuals older than 85, screening is not recommended at all; individual circumstances may vary and screening should be done per a doctor's recommendation (USPSTF, 2008).

Cervical Cancer

Cervical cancer is the third most common cause of cancer incidence in women worldwide. In the US alone, about 12,990 diagnosed cases and 4,120 deaths are estimated for 2016 (Arbyn et al., 2011; ACS, 2016). Cervical cancer is caused by certain types of Human Papillomavirus (HPV), with 70% of cases caused by types 16 and 18 (zur Hausen, 2000; Cogliano et al., 2005; Watson et al., 2008). HPV is a very common sexually transmitted infection, infecting mucosal and skin tissues, with low-risk types causing warts and high-risk types causing cancer. While most infections resolve on their own, a subset of women with high-risk types develop persistent HPV infections, which can lead to cervical cancer. HPV is also associated with cancer of the vulva, vagina, penis, anus, and oropharynx (Cogliano et al., 2005; Watson et al., 2008).

While HPV infection is most common among younger women, cervical cancer affects women in midlife, before age 50, which is earlier than other cancers (Arbyn et al., 2011). Cofactors for cervical cancer include smoking, being overweight, inadequate fruit and vegetable consumption, parity, early full term pregnancy, as well as long-term oral contraceptive use (Danaei et al., 2005). Other sexually transmitted infections, unprotected sex with multiple partners, early sexual debut, and immunosuppression due to HIV infection or drug therapy are also associated with cervical cancer (Watson et al., 2008). In the United States, Hispanic and African-American women have higher rates of incidence and mortality (Watson et al., 2008).

Effective prophylactic vaccines have been developed, including the bivalent Cervarix (by GlaxoSmithKline) targeting HPV types 16 and 18; the quadrivalent Gardasil (by Merck) targets HPV types 6, 11, 16 and 18 and was approved by the US Food and Drug Administration in 2006 (CDC, 2014). Currently, the vaccines are targeted toward youth and adolescents, prior to sexual debut and subsequent exposure to HPV. Regular screenings, early detection, and early treatment are the primary mechanism to reduce mortality and have been effective in reducing cervical cancer mortality by 50% in the last 30 years (ACS, 2016; Watson et al., 2008). The US Preventive Services Task Force (USPSTF) recommends regular screening for cervical cancer through cytology (Pap smear) every three years beginning at age 21 and continuing until age 65 years. Women age 30-65 may alternatively do cytology coupled with human papillomavirus (HPV) testing every five years. Screening for

cervical cancer prior to age 21 of after age 65 (for women who have been screened regularly) is not recommended by USPSTF. (USPSTF, 2012)

Methods

Data Sources

Data on cancer incidence and mortality were from the 2012 United States Cancer Statistics Data, which combines data from the National Program of Cancer Registries reported to the Centers for Disease Control and Prevention (CDC) and registries in the Surveillance, Epidemiology, and End Results Program (SEER) reported to the National Cancer Institute (NCI) (U.S. Cancer Statistics Working Group, 2015). This database extracts incidence data from medical records that were sent by health care facility staff to state or regional cancer registries; this analysis used incident cancer cases from 2012. Colorectal cancer incidence data from Nevada and cervical cancer incidence data from Nevada and Vermont were missing for 2012, so sample sizes were 50 and 49, respectively (including the District of Columbia). Race and age demographics were from the 2012 Intercensal Estimates of the Resident Population for the United States (US DHHS, 2012; US Census, 2013).

State-level information on health behaviors for adults were from landline and cellular telephone surveys conducted in the CDC's annual Behavioral Risk Factor Surveillance System (BRFSS) (CDC, 2012). From the 2012 BRFSS, state level

aggregates of adult (18+ years old) current smoking status, obesity, and binge drinking were used in analysis. State-level data on physically active adults from the 2011 BRFSS and adult fruit and vegetable consumers from the 2009 BRFSS were also used, as these were the most recent data on these risk factors. These state level aggregates were from the CDC's Sortable Stats report, which included percentage of adults who fell into each category, by state (CDC, 2016). Current smokers were adults who reported smoking every or some days, divided by all respondents who responded to the question, "Do you now smoke cigarettes every day, some days, or not at all?". Binge drinkers were males who reported having five or more drinks on one occasion, or females having four or more drinks on one occasion, in the past 30 days, divided by total respondents who reported drinking in the past 30 days (including 0 drinks, or non-drinkers). BMI was calculated based on self reported weight and height, and percentage of obese adults defined as people with BMI of 30 or greater, divided by all adults with a valid calculated BMI. Adults who reported 150 minutes per week or more of light or moderate physical activity, 75 minutes per week or more of vigorous activity, or a combination were considered to be physically active, with the denominator being all adult respondents. Adult nutrition was measured by dividing adults who reported consuming fruits and vegetables five or more times per day divided by total respondents who reported eating fruit and vegetables consumption per day (including 0 servings or non-consumers).

Condom use by state was from Simmons LOCAL, a national consumer survey administered to adults age 18 and older in 210 designated market areas using samples averaging 30,000 per market. Condom use was assessed by the single question, "Do you use condoms?" in the survey (Experian Simmons, 2012). While there was no recall period or time frame for this question, there were follow-up questions regarding primary brands of condoms used; this level of brand specificity was not used in this analysis.

Spatial Analysis

All spatial analysis was conducted in ArcGIS 10.3.1 (ESRI, 2015). Data for the US and state borders came from the 2012 United States Census (available from: https://www.census.gov/geo/maps-data/data/tiger-line.html). The shapefile was projected to the NAD 1983-2011 Contiguous USA Albers projection, then predictors and outcome variables from SAS were matched to the respective states by FIPS code. Descriptive maps were created for age-adjusted colorectal and cervical cancer incidence, as well as reported condom use, physical activity, obesity, smoking and fruit and vegetable consumption. Categorization was based on Jenks natural breaks, which creates classifications based on the data, in order to minimize variance from the mean within groups. The states missing data were noted on the maps.

Bivariate association with cancer incidence

All statistical analyses were conducted with SAS 9.4 (Cary, N.C., 2012). Sampling weights were not used in these analyses, as only state-level aggregates were being utilized. Linear regression models were fit with the regression procedure in SAS, which estimates parameters by the ordinary least squares method.

The outcome variables for the two linear models were age-adjusted incidence rate for colorectal cancer per 100,000 (male and female) and cervical cancer per 100,000. The exposure variable for both models was percentage of reported condom users. The predictor variables that were considered were state percentages of current smokers, physically active adults, binge drinkers, and obese adults. Demographic percentages for race/ethnicity and age categories (18-49, 50-64, and >65 years old) were also considered, as well as male population for colorectal cancer. Prior to conducting linear regression, mean cancer incidence rates, as well as mean percentage of condom use and demographic controls were obtained for states and the nine geographic regions of the US. Correlations between the outcomes and predictors were also assessed.

Since cancer incidence is a continuous outcome, the first assumption of linear regression was met. The second assumption of linear regression, independent and identically distributed error terms, was verified through chi-squared test of moment specification (SPEC option in PROC FREQ) and the Durbin-Watson statistic.

Simple linear regression was conducted with each predictor for each outcome to assess bivariate linear relationships and investigate influential outliers. For both outcomes, there was an influential outlier for condom use; Washington, D.C. reports the highest condom use in the sample at 28.6%, with Maryland and Georgia as the next highest states, both with about 19% condom use. This observation was not removed due to the plausibility of the value and the small sample size, although for multiple linear regression, models were run with both the full sample and excluding DC.

Multivariable association with cancer incidence

There was insufficient data to fit all the parameters of the model with all predictors, so age categories were dropped from the model; given that the outcome were age-adjusted incidence rates, age was already sufficiently controlled for. For the purpose of this analysis, only the proportion of Black and Hispanic populations in each state were included, because these race/ethnicity groups were reported to be associated with cervical or colorectal cancer incidence in the literature.

Multiple linear regression for colorectal cancer incidence included nine predictors: proportions of condom users, current smokers, male population, physically active adults, regular fruit and vegetable consumers, binge drinkers, obese adults, Black or African-American, and Hispanic. Multiple linear regression for cervical cancer incidence included these same predictors, with the exception of male population. Two-way interaction terms for condom use and each of the other predictors were

created and included in the initial model, to account for the possibility of effect modification with condom use and another predictor. For both types of cancer, multicollinearity was assessed for the full models with all predictors and all two-way interaction terms. For both colorectal and cervical cancer, all interaction terms were dropped from both models as their inclusion produced collinearity and did not result in a meaningful change in adjusted R^2 values. Removal of the interaction terms reduced the VIF for all remaining parameters in both models.

Model selection was conducted by identifying predictors that had been shown to be associated with each of the cancer types in the literature and including those in the final model. For colorectal cancer, this meant that all nine predictors were included in the final model. For cervical cancer, proportions of condom users, current smokers, physically active adults, obese adults, Black or African-American race, and Hispanic ethnicity were associated with cervical cancer in the literature and thus these six were automatically included in the model. Regular fruit and vegetable consumers as well as binge drinkers were not established predictors and were considered for inclusion in the model through forward selection. However, neither of these variables fit the inclusion criteria of $p=0.05$ and were thus excluded from the final cervical model. Regression was done on both the full sample and excluding Washington, D.C. to examine the effect of a potentially influential outlier. However, this changed parameter estimates and adjusted R^2 values only modestly and did not change significance of p-values or conclusions drawn. The final models reported in

the results thus reflect the full sample. Regression diagnostics were then conducted on the selected model to determine model fit.

Results

Table 1 shows the mean and standard deviation of the outcome and predictor variables for the entire US as well as for nine geographic regions. The spatial distribution of these variables by state are represented in Figures 1 through 8.

Colorectal Cancer Incidence

Results of bivariate simple linear regression for age adjusted colorectal cancer incidence are presented in Table 2. In bivariate analyses, condom use was not associated with colorectal cancer incidence (p-value= 0.2266) nor did it predict a high proportion of colorectal cancer incidence (R^2= 0.0303). Smoking had a positive linear association with colorectal cancer incidence in bivariate analysis, indicating a hazardous association. Higher physical activity and fruit and vegetable consumption were negatively correlated with colorectal cancer incidence, indicating a protective effect. Hispanic race had a negative association with colorectal cancer incidence. Proportion of male population, African Americans, and binge drinking was not associated with colorectal incidence.

The final multivariable linear regression model for colorectal cancer incidence is presented in Table 3; the only significant predictors are physical activity (a negative

or protective association) and binge drinking (a positive or hazardous association). Condom use was not associated with colorectal cancer in the multivariable model (p-value= 0.5568) The adjusted R^2 value for the multivariable model was 0.4531.

Cervical Cancer Incidence

Results of simple linear regression for age adjusted cervical cancer incidence are presented in Table 4. In bivariate analyses, condom use was not associated with cervical cancer incidence (p-value= 0.3796) nor did it predict a high proportion of colorectal cancer incidence (R^2= 0.0165). Proportion of current smokers, obese adults, and African American population were positively associated with cervical cancer incidence, indicating a hazardous association. Higher physical activity and fruit/vegetable consumption, were negatively associated with cervical cancer, indicating a protective association. Proportion of binge drinkers was also negatively associated with incidence. Proportion of Hispanic population was not associated with incidence.

Multivariable linear regression results for cervical cancer incidence are presented in Table 5. Proportion of current smokers and Hispanic population were positively associated with cervical cancer incidence, when controlling for other predictors. In multiple linear regression, no other predictors were significant, including condom use (p-value= 0.9453), indicating no association with cervical cancer incidence. The adjusted R^2 value for the multivariable model was 0.3696.

Discussion:

Conclusions:

The aim of the study was to address concerns about possible carcinogenic risk caused by nitrosamine exposure from condoms. In all bivariate regressions, there was no association between condom use and age-adjusted colorectal or cervical cancer incidence in the US. After adjusting for risk factors and protective covariates that are established in the literature for cervical and colorectal cancer, there was also no association with condom use and age-adjusted cancer incidence in multivariable models.

The models produced in these analyses had moderate predictive value for colorectal and cervical cancer incidence, with the adjusted R^2 values for both final models between 0.3 and 0.5. There were some significant results in bivariate simple linear regressions that were different from what was expected based on the literature, but these relations did not hold after controlling for potential confounding factors. For instance, a negative association between Hispanic population percentage and colorectal cancer incidence was observed; this association was no longer significant when adjusting for more than one variable. There was also a negative association between adult binge drinkers and cervical cancer incidence, although binge drinking was not an established predictor or protective factor for cervical cancer in the literature, nor did it meet the inclusion criteria for the final multivariable model.

Limitations:

Since this is an ecological study, any significant findings would be limited to association and not causation. The ecological design of the study is a shortcoming: findings at the state level may not hold true at finer scales and the predictive model may not be generalizable to individuals. Small sample size limited not only the size of the model, as too many predictors made beta estimates unstable, but also precluded the possibility of creating a validation subset to compare the predictive capabilities of the model. Small sample size also increased the variance of estimates and may have rendered non-significant certain predictors that would have contributed significantly to the model in a larger sample; this may have resulted in known predictors like obesity and smoking becoming non-significant in multivariable models. The Durbin-Watson statistic to test for independent and identically distributed errors for both models were less than the threshold of 2.0 (Colorectal= 1.255; Cervical=1.904); however, the statistic is not necessarily valid for small sample sizes so one of the underlying assumptions of linear regression may be challenged. Despite these limitations, relations between variables previously found to be associated with cancer incidence, such as physical activity and smoking, were confirmed in our analysis, indicating that our design had sufficient power to detect some of the most prominent risk factors for cancer.

The reliance on self-reported measures of height and weight (to calculate BMI), smoking, frequency of exercise and fruit/vegetable consumption, as well as drinking habits may also introduce social desirability bias if respondents answer survey

questions so as to be more concordant with healthy lifestyle expectations. However, BRFSS surveys are well established, and the survey questions and enumerators are likely designed or trained to reduce respondent bias. To increase sensitivity in exposure to certain predictors for this particular analysis, it may have been more useful to include percentage of adults who are overweight as well as obese. Similarly, it may have been more informative to include former smokers along with current smokers to capture lifetime exposure to smoking, or to limit analyses to non-smokers only in a non-ecological study. Smoking is an important confounder in this analysis, as it is associated with not only both cancer types but is also a source of nitrosamine exposure (Harrison et al., 2006; Hecht et al., 2016). Tobacco users who do not smoke tobacco but use snuff would not be counted as smokers in this analysis but are still exposed to carcinogenic 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) (Hecht et al., 2016).

The conclusions of this analysis are contingent on the accuracy and representativeness of the data on condom usage. The way the indicator was measured, through the question "Do you use condoms," is a more general and inclusive measure of condom usage, compared to use at a specific time point, like at last sexual encounter. However, the non-specific nature of the question opens it up to interpretation by the respondent and does not delineate frequent or recent condom use. The sampling methodology may also have created biases if it it was not representative. While a very large sample of the US, the Experian SimmonsLOCAL sampling is not designed for public health studies, but rather intended to create

consumer profiles for marketing and sales purposes. The choice to use the consumer survey was an unorthodox one, driven by lack of free and publicly available data on condom usage by state.

Future directions

In general, further population-based studies investigating the association between condom use and cancer incidence may be justified, especially for a larger sample size and with a more established measure of condom usage. A decision was made not to incorporate data on HPV vaccination into the models; Although HPV infection causes cervical cancer, and prevention through vaccination is effective, the population that was being diagnosed with cancer in 2012 would most likely not have received the vaccination prior to HPV exposure given the recent FDA approval at that time. However, future analyses of HPV cancer incidence should take into account HPV vaccination rates when controlling for cervical cancer.

This study did not find any ecological association between condom use (with putative nitrosamine exposure) and cervical or colorectal cancer incidence in the US. Further study may be warranted to better establish the degree of nitrosamine carcinogenicity and potential mechanisms in humans; however, certain means of exposure, like rubber manufacturing work or long-term latex glove use, may be more intensive or high-risk, and possibly ought to be prioritized in research agendas. There is a body of scientific evidence to support presence of nitrosamines in multiple sources that may affect humans, as well as carcinogenicity of many

nitrosamine types in animal models. However, Bryan, et al. cautioned against direct extrapolation of animal models for human carcinogenicity, given the differences in physiology and dietary needs between humans and animal models (Bryan et al., 2012). Epidemiologic cancer studies that deal with the many forms of nitrosamine exposure are incredibly heterogeneous in terms of methodology as well as strength and cohesiveness of evidence.

In risk assessments for condom-associated nitrosamine exposure, it is important to note that condom efficacy as a contraceptive measure and in prevention of HIV/STI transmission (including HPV) is well established, and has substantial health benefits. The present study found no evidence of an association between condom use and cancer incidence; physicians and practitioners should continue to recommend condoms without hesitation.

Appendix

Figure 1

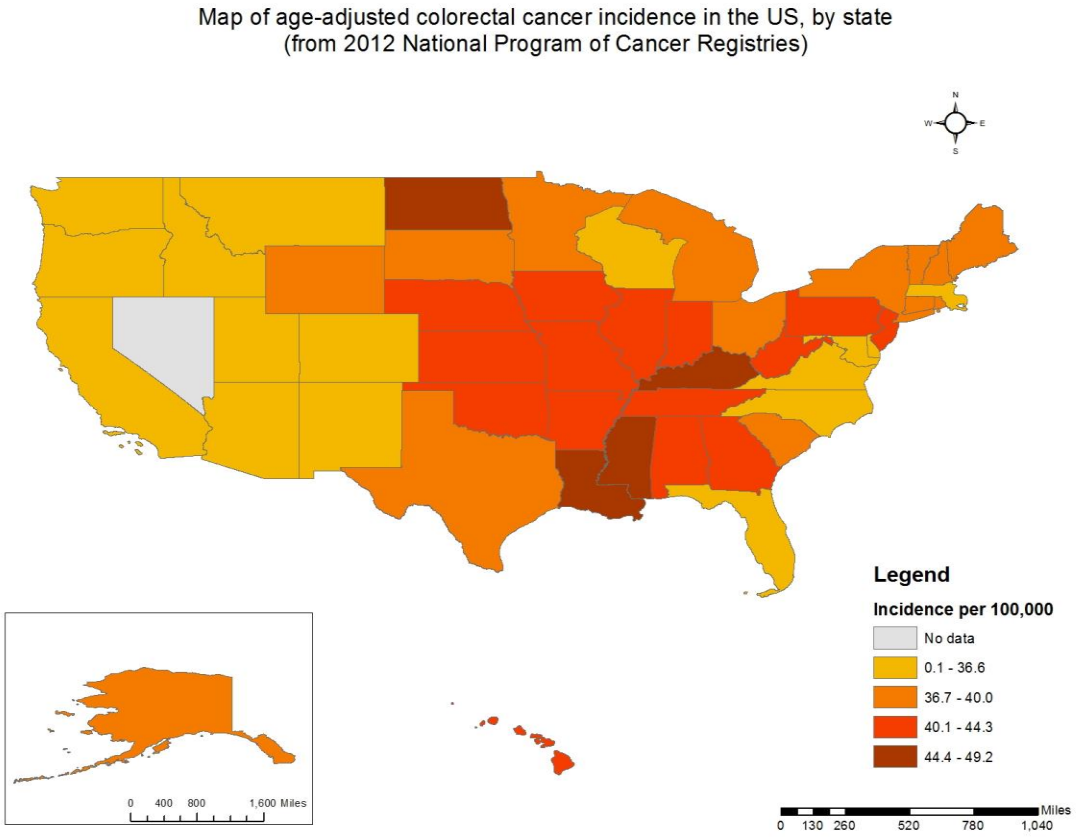


Figure 2

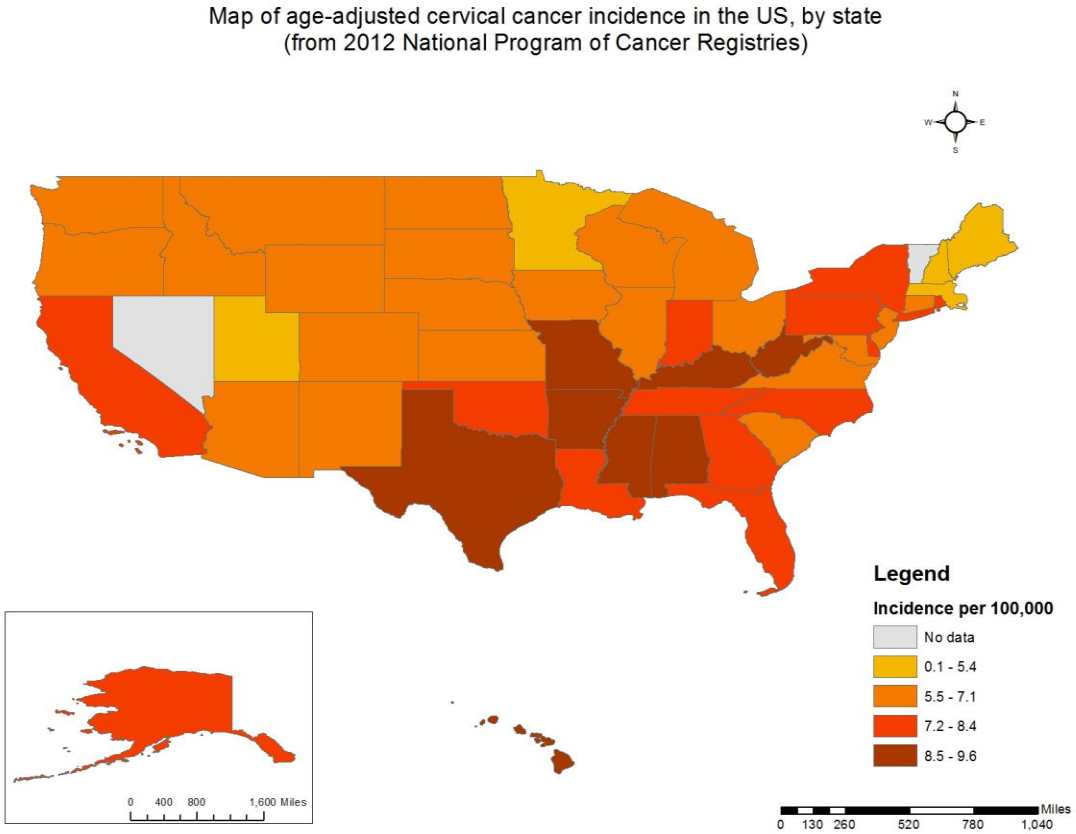

Map of age-adjusted cervical cancer incidence in the US, by state
(from 2012 National Program of Cancer Registries)
N
W
E
S
Legend
Incidence per 100,000
No data
0.1 - 5.4
5.5 - 7.1
7.2 - 8.4
8.5 - 9.6
0 400 800 1,600 Miles
0 130 260 520 780 1,040 Miles

Figure 3

Map of condom use in the US, by state (based on Experian 2012 SimmonsLOCAL Consumer Survey)

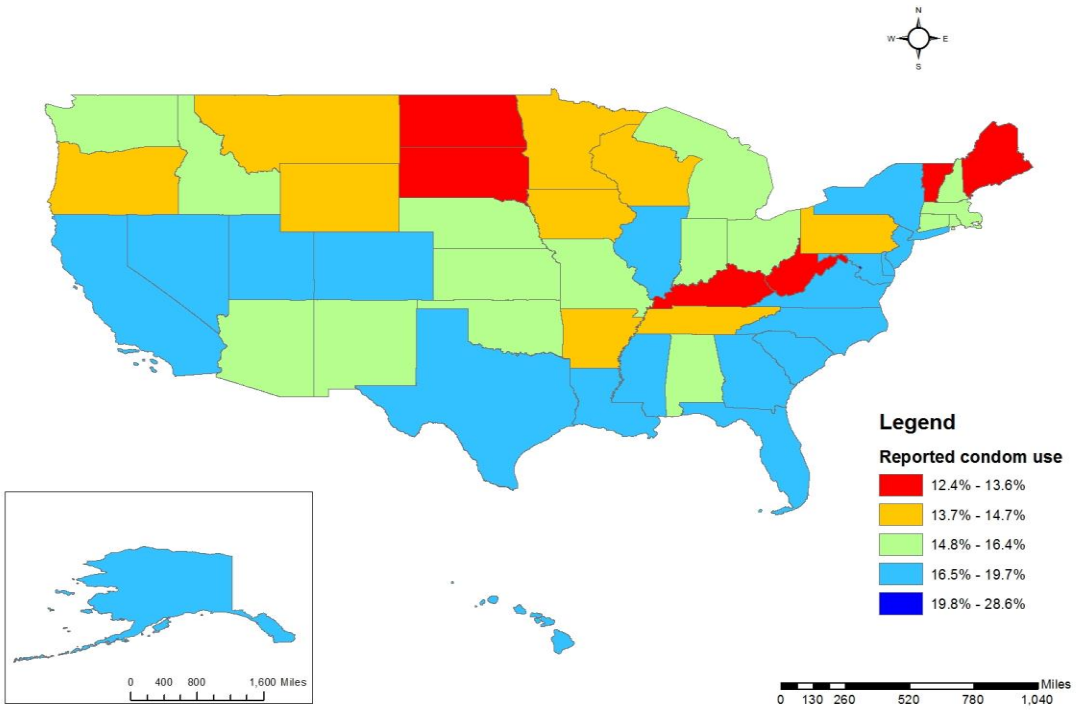


Figure 4

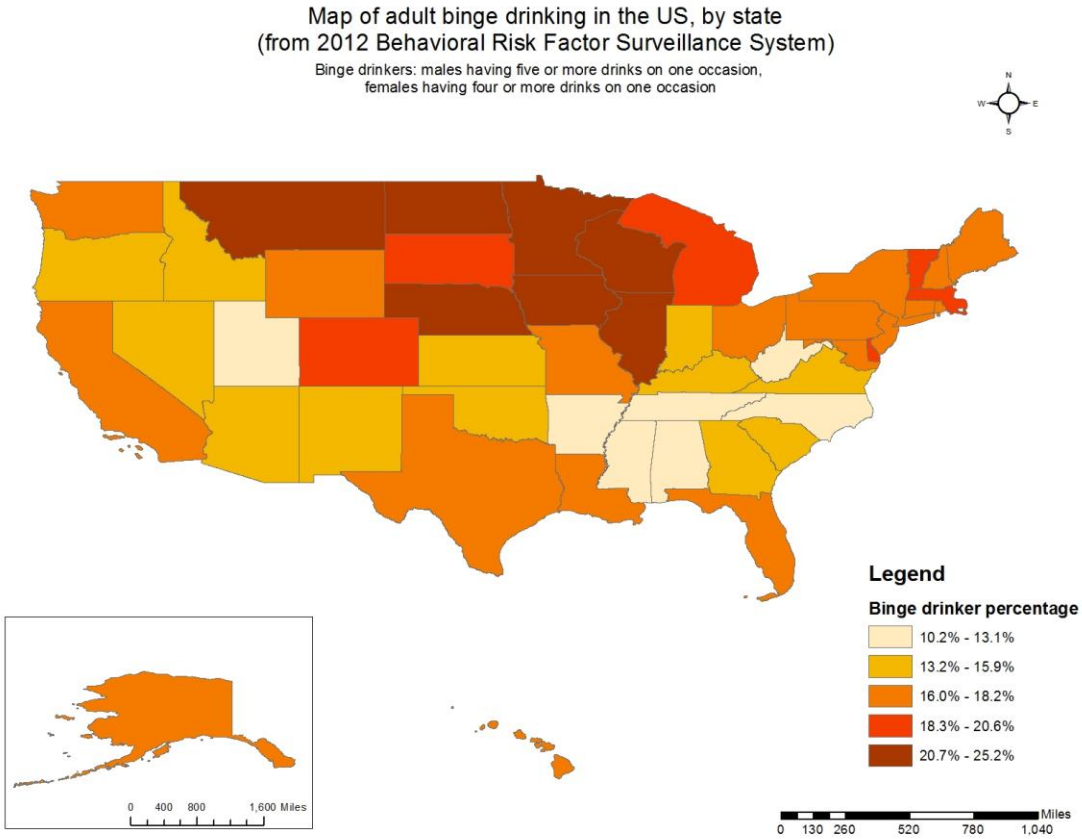

Map of adult binge drinking in the US, by state
(from 2012 Behavioral Risk Factor Surveillance System)
Binge drinkers: males having five or more drinks on one occasion, females having four or more drinks on one occasion
N
W
E
S
Legend
Binge drinker percentage
10.2% - 13.1%
13.2% - 15.9%
16.0% - 18.2%
18.3% - 20.6%
20.7% - 25.2%
0 400 800 1,600 Miles
0 130 260 520 780 1,040 Miles

Figure 5

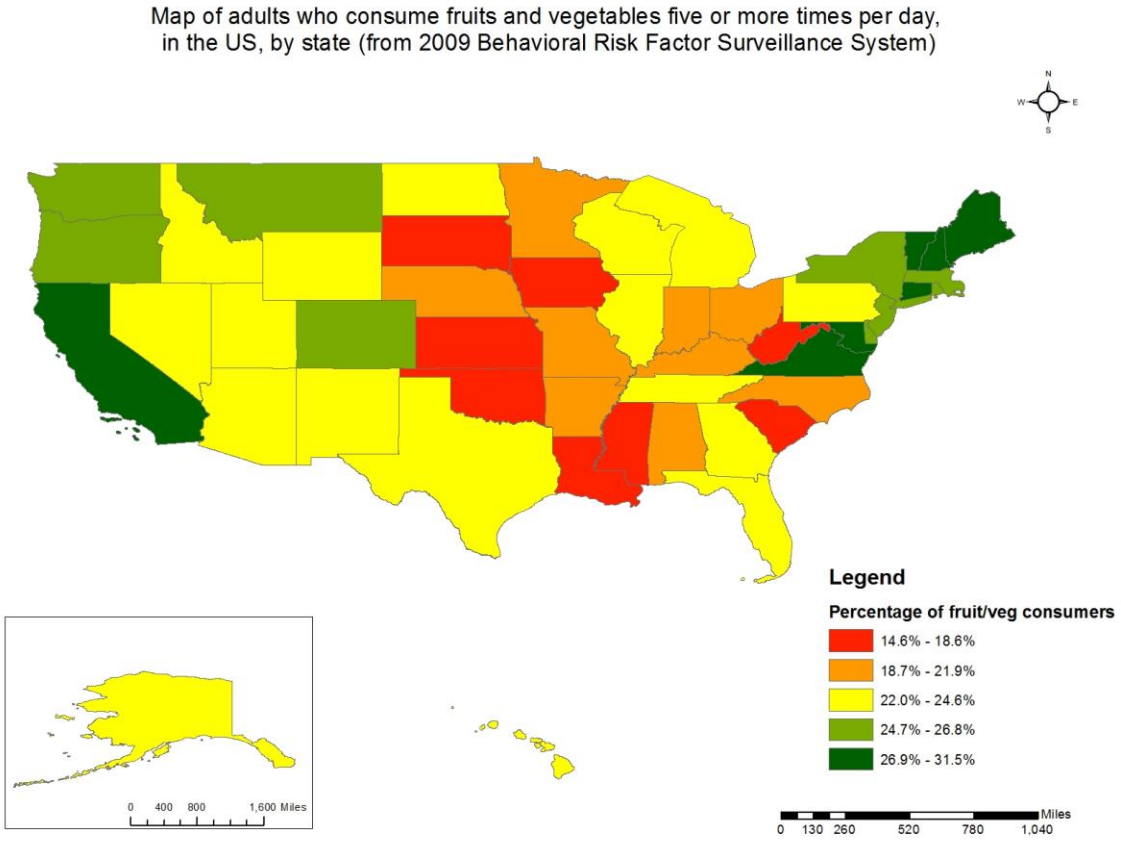

Map of adults who consume fruits and vegetables five or more times per day, in the US, by state (from 2009 Behavioral Risk Factor Surveillance System)
N
W
E
S
Legend
Percentage of fruit/veg consumers
14.6% - 18.6%
18.7% - 21.9%
22.0% - 24.6%
24.7% - 26.8%
26.9% - 31.5%
0 400 800 1,600 Miles
0 130 260 520 780 1,040 Miles

Figure 6

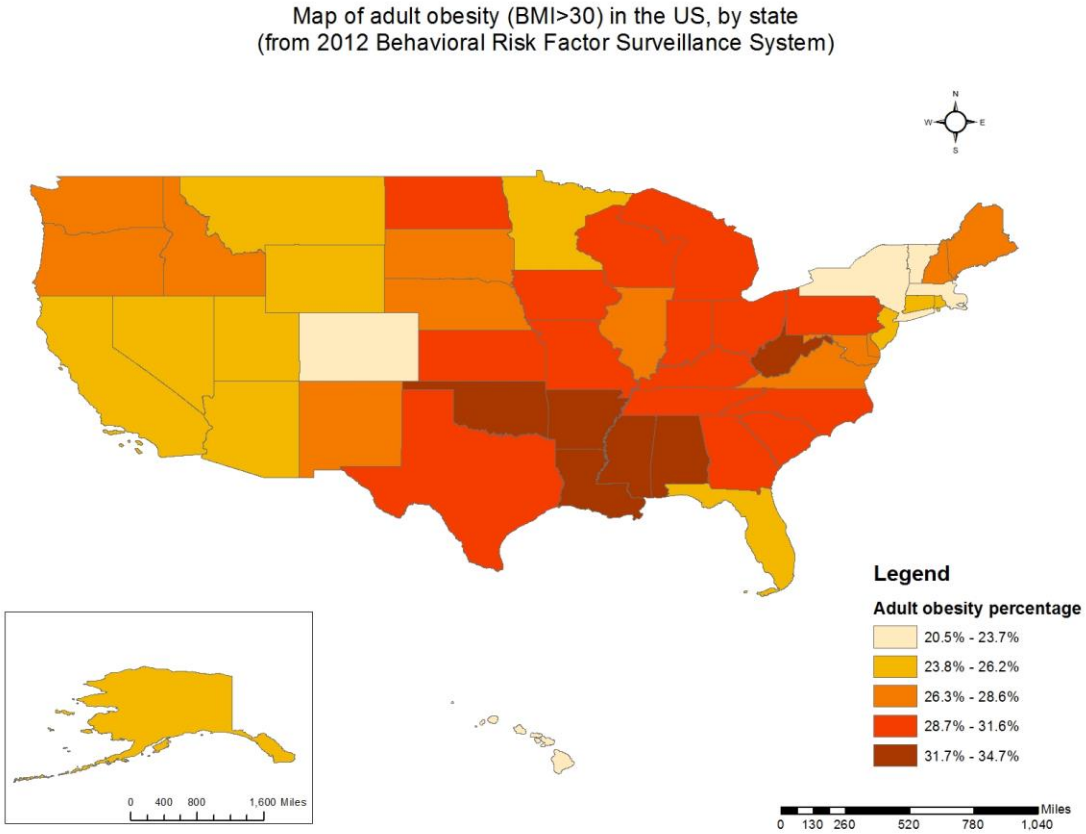

Map of adult obesity (BMI>30) in the US, by state
(from 2012 Behavioral Risk Factor Surveillance System)
N
W
E
S
Legend
Adult obesity percentage
20.5% - 23.7%
23.8% - 26.2%
26.3% - 28.6%
28.7% - 31.6%
31.7% - 34.7%
0 400 800 1,600 Miles
0 130 260 520 780 1,040 Miles

Figure 7

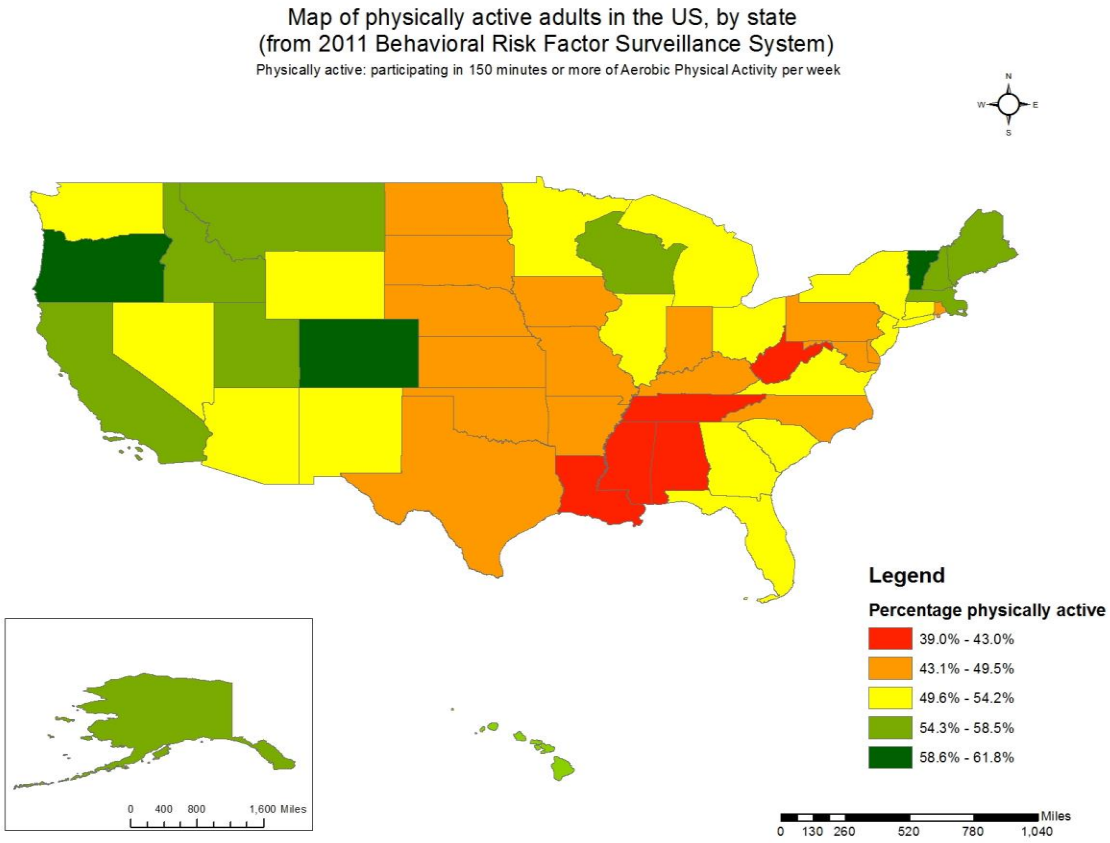

Map of physically active adults in the US, by state
(from 2011 Behavioral Risk Factor Surveillance System)
Physically active: participating in 150 minutes or more of Aerobic Physical Activity per week
N
W
E
S
Legend
Percentage physically active
39.0% - 43.0%
43.1% - 49.5%
49.6% - 54.2%
54.3% - 58.5%
58.6% - 61.8%
0 400 800 1,600 Miles
0 130 260 520 780 1,040 Miles

Figure 8

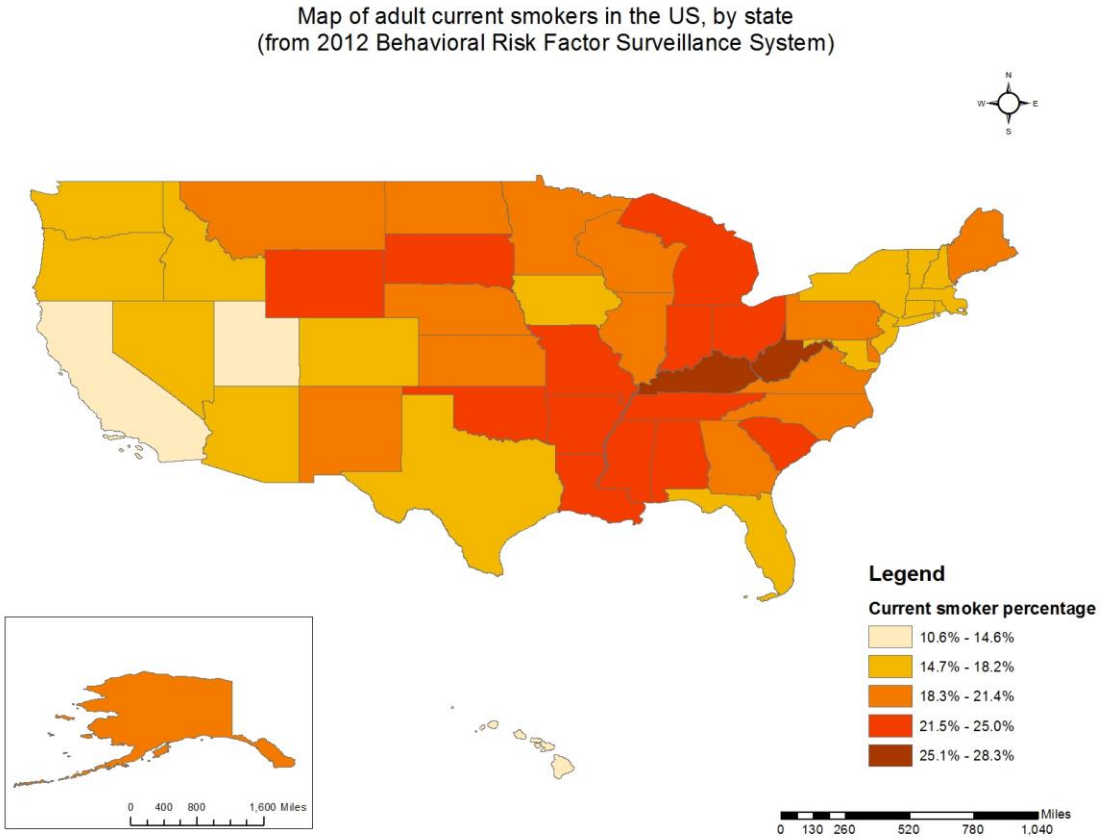

Map of adult current smokers in the US, by state
(from 2012 Behavioral Risk Factor Surveillance System)
N
W
E
S
Legend
Current smoker percentage
10.6% - 14.6%
14.7% - 18.2%
18.3% - 21.4%
21.5% - 25.0%
25.1% - 28.3%
0 400 800 1,600 Miles
0 130 260 520 780 1,040
Miles

Table 1

Table 1: Descriptive Statistics for Colorectal (n=50) and Cervical (n=49) Cancer Incidence and Behavioral and Demographic Predictors in the United States and Nine Regions

	Entire US		East North Central		East South Central		Middle Atlantic		Mountain		New England		Pacific		South Atlantic		West North Central		West South Central	
	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev	Mean Incidence (per 100,000)	Std Dev
Age-adjusted colorectal cancer	39.37	4.333	39.70	2.879	45.53	3.788	41.30	1.992	33.93	2.212	37.83	1.398	37.78	2.835	37.88	3.406	42.56	3.514	42.90	4.441
Age-adjusted cervical cancer	7.19	1.351	6.66	0.577	9.08	0.519	7.50	0.346	6.26	0.750	5.58	1.486	7.34	1.266	7.70	1.063	6.84	1.296	8.65	0.480
	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev	Mean %	Std Dev
Condom user	16.12%	0.025	15.67%	0.012	15.22%	0.017	16.74%	0.017	16.10%	0.017	14.91%	0.012	16.61%	0.014	18.59%	0.040	14.09%	0.011	16.38%	0.014
Current smoker	19.85%	0.036	21.92%	0.021	25.25%	0.018	18.30%	0.022	17.54%	0.032	17.30%	0.014	16.56%	0.027	20.47%	0.032	20.44%	0.019	22.83%	0.028
Male	49.33%	0.008	49.18%	0.003	48.77%	0.003	48.68%	0.001	50.14%	0.004	48.85%	0.004	50.31%	0.010	48.64%	0.005	49.83%	0.005	49.29%	0.003
Adults who do a minimum of 150 minutes of Physical Activity weekly	51.23%	0.054	52.04%	0.037	42.05%	0.030	51.40%	0.016	55.26%	0.031	54.93%	0.034	57.98%	0.022	50.06%	0.039	48.61%	0.025	45.18%	0.022
Adults who eat at least 5 servings of fruits and vegetables daily	23.15%	0.037	21.88%	0.009	20.38%	0.023	25.77%	0.012	24.12%	0.009	27.63%	0.011	25.20%	0.016	23.83%	0.047	19.71%	0.022	18.93%	0.035
Adult Binge Drinkers	17.08%	0.033	19.98%	0.032	12.65%	0.014	17.53%	0.004	16.12%	0.032	18.07%	0.010	16.82%	0.009	15.93%	0.034	20.50%	0.027	14.73%	0.019
Obese adults (BMI > 30)	27.97%	0.034	30.08%	0.012	32.50%	0.014	25.77%	0.024	24.86%	0.020	25.60%	0.019	25.68%	0.013	28.12%	0.033	28.86%	0.015	32.65%	0.022
Race/Ethnicity																				
Black or African-American	11.02%	0.107	11.16%	0.031	21.95%	0.108	12.67%	0.016	2.14%	0.018	4.20%	0.033	3.29%	0.015	23.98%	0.116	4.77%	0.032	16.56%	0.093
Hispanic	10.79%	0.098	7.34%	0.046	3.74%	0.008	14.28%	0.058	19.71%	0.136	7.30%	0.054	15.58%	0.115	9.25%	0.055	5.77%	0.030	14.70%	0.136

Table 2

Table 2: Results of Simple Linear Regression for 2012 Age-Adjusted Colorectal Cancer Incidence in the United States (missing Nevada)

	Simple Linear Regression (n=50)			
Predictor	**Beta Estimate**	**t-test (df)**	**p-value**	**R-squared**
Condom users	-29.21	-1.22 (48)	0.2266	0.0303
Current smoker	72.54	5.27 (48)	<.0001*	0.3667
Male	-44.04	-0.57 (48)	0.5702	0.0068
Physically active adults	-47.32	-5.12 (48)	<.0001*	0.3529
Regular Fruit and Vegetable Consumers	-56.22	-3.91 (48)	0.0003*	0.2412
Adult Binge Drinkers	2.37	0.13 (48)	0.8986	0.0003
Obese adults (BMI > 30)	76.06	5.16 (48)	<.0001*	0.3564
Race/Ethnicity				
Black/African-American	10.25	1.84 (1)	0.0712	0.0662
Hispanic	-18.94	-3.29 (1)	0.0019*	0.1842

*Significant at alpha=0.05

Table 3

Table 3: Results of Multiple Linear Regression for 2012 Age-Adjusted Colorectal Cancer Incidence in the United States (n=50; missing Nevada) [1]

	Beta Estimate	95% Confidence Limits		t-test (df=6)	p-value
Intercept	-4.64	-96.43	87.14	-0.10	0.9191
Condom users	26.06	-62.82	114.94	0.59	0.5568
Current smoker	24.81	-20.10	69.71	1.12	0.2709
Obese adults	37.19	-23.71	98.10	1.23	0.2243
Physically active adults	-35.89	-68.73	-3.04	-2.21	0.0330*
Vegetable consumers	9.37	-34.30	53.04	0.43	0.6668
Adult Binge Drinkers	38.76	6.78	70.74	2.45	0.0188*
Percentage of pop: Black	-1.49	-26.23	23.24	-0.12	0.9034
Percentage of pop: Hispanic	-7.04	-18.47	4.39	-1.24	0.2207
Male	70.91	-107.16	248.98	0.80	0.4257

[1] Model R^2= 0.5535; adjusted R^2= 0.4531
*Significant at alpha=0.05

Table 4

Table 4: Results of Simple Linear Regression for 2012 Age-Adjusted Cervical Cancer Incidence in the United States (missing Nevada and Vermont)

Predictors	Simple Linear Regression (n=49)			
	Beta Estimate	t-test (df)	p-value	R-squared
Condom users	6.71	0.89 (1)	0.3796	0.0165
Current smoker	18.60	3.94 (1)	0.0003*	0.2487
Physically active adults	-13.84	-4.52 (1)	<.0001*	0.3028
Regular Fruit and Vegetable Consumers	-12.81	-2.58 (1)	0.013*	0.1243
Adult Binge Drinkers	-13.73	-2.53 (1)	0.015*	0.1195
Obese adults (BMI > 30)	17.21	3.27 (1)	0.002*	0.1853
Race/Ethnicity				
Black or African-American	5.16	3.14 (1)	0.0029*	0.1733
Hispanic	-0.13	-0.06 (1)	0.9487	0.0001

*Significant at alpha=0.05

Table 5

Table 5: Results of Multiple Linear Regression for 2012 Age-Adjusted Cervical Cancer Incidence in the United States (N=49; missing Nevada and Vermont)[1]

	Beta Estimate	95% Confidence Limits		t-test (df=6)	p-value
Intercept	0.35	-9.74	10.43	0.07	0.9453
Condom users	14.09	-13.50	41.68	1.03	0.3085
Current smoker	20.50	5.50	35.51	2.76	0.0086*
Vegetable consumers	-5.47	-18.34	7.40	-0.86	0.3959
Obese adults	4.00	-15.04	23.05	0.42	0.6735
Percentage of pop: Black	1.38	-5.06	7.82	0.43	0.6668
Percentage of pop: Hispanic	4.22	0.50	7.95	2.29	0.0274*

[1]Model R^2= 0.4484; adjusted R^2= 0.3696

*Significant at alpha=0.05

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