Cancer Epidemiology Used in Policy Questions

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Erin E. Cook, MPH

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Dissertation Advisor: Michelle D. Holmes, MPH, MD, DrPH Erin E. Cook, MPH

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Abstract

This dissertation sought to answer policy questions concerning cancer using techniques and skills from epidemiology for three studies. First, trends in cancers associated with human papillomavirus (HPV) can help public health providers examine where to target prevention. Second, understanding the impact that legislation regarding HPV vaccination and education can have on teen sexual behaviors can also help inform policy. Third, understanding the burden that a breast cancer diagnosis has on young women (under age 45) in terms of income and employment allows providers to understand what populations may be vulnerable to changes.

To answer these questions multiple methods were used. For the first study, data from the Massachusetts Cancer Registry were used to assess trends in HPV-associated cancers using Joinpoint regression. The second study used publicly available data from the Youth Risk Behavior Surveillance System (YRBSS). Difference-in-difference techniques were used to look at the impact of legislation on teen sexual behaviors. Lastly, we used data from the Young and Strong intervention trial to examine how stress, anxiety, and depression impacted changes in income status for young women with breast cancer using multinomial logistic regression models.

Our first study found that the incidence rate of cervical cancer has been decreasing in Massachusetts while the incidence rate of oropharyngeal cancer has been increasing. Promoting cervical cancer screening and HPV vaccination will be important to prevent these cancers. Our second study found that enacting HPV legislation did not have any negative impacts on teen sexual behaviors of recent sexual intercourse or condom use during last intercourse. Concerns

that HPV policies may negatively influence teen sexual behaviors should not be used when deciding whether to enact legislation. Lastly, we found that young women who had lower incomes and higher stage breast cancer had a higher risk of losing income than maintaining the same income under $100,000. Stress, anxiety and depression did not have an impact on change in income. These women represent a subset of young breast cancer patients that may be require more assistance during cancer treatment and survivorship.

Cancer epidemiology can be used to answer policy questions concerning screening and prevention as well as issues related to survivorship for a wide range of cancer subtypes.

Abbreviations

APC = Annual Percent Change

BRFSS = Behavioral Risk Factor Surveillance System

CDC = Centers for Disease Control and Prevention

CES-D = Center for Epidemiologic Studies Depression Scale

CHIP = Children's Health Insurance Program

CI = Confidence Interval

FDA = Food and Drug Administration

HADS = Hospital Anxiety and Depression Scale

HPV = Human Papillomavirus

MCR = Massachusetts Cancer Registry

MDPH = Massachusetts Department of Public Health

MRVRS = Massachusetts Registry of Vital Records and Statistics

PAI = Physical Activity Intervention

PSS = Perceived Stress Scale

RR = Risk Ratio

US = United States

YRBSS = Youth Risk Behaviors Surveillance System

YWI = Young Women's Intervention

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Trends of Two HPV-Associated Cancers in Massachusetts: Cervical and Oropharyngeal Cancer

Erin E. Cook, MPH; Susan T. Gershman, MS, MPH, PhD, CTR; Jane J. Kim, PhD; Rulla M. Tamimi, ScD; R. Monina Klevens, DDS, MPH; Michelle D. Holmes, MPH, MD, DrPH. Trends of Two HPV-Associated Cancers in Massachusetts: Cervical and Oropharyngeal Cancer. *Cancer Causes & Control* 2018. Online https://doi.org/10.1007/s10552-01801016-1.

ABSTRACT

Purpose: To understand trends in the incidence and mortality of two human papillomavirus (HPV)-associated cancers, cervical and oropharyngeal cancer, in Massachusetts.

Methods: From 2004-2014, the Massachusetts Cancer Registry recorded 3,996 incident cases of oropharyngeal cancer and 2,193 incident cases of cervical cancer. Mortality data were obtained from the Massachusetts Registry of Vital Records and Statistics from 2008-2014. Rates were age-standardized to the 2000 US population and trends were assessed using joinpoint regression.

Results: While the incidence rate of cervical cancer (5.46 per 100,000) decreased by 2.41% annually (p=0.004), the incidence rate of oropharyngeal cancer among males (7.85 per 100,000) increased by 2.82% annually (p=0.0002). Mortality rates for both cancers decreased from 2008-2014 but were not statistically significant (Cervical -3.73% annually, p=0.29; Oropharyngeal -1.94% annually, p=0.44).

Conclusion: The rising incidence rate of oropharyngeal cancer in men and the decreasing, but relatively high, incidence rate of cervical cancer in women highlight the need for further screening and prevention by HPV vaccination in Massachusetts.

INTRODUCTION

Persistent infection with a high risk type of human papillomavirus (HPV) is known to cause cervical, oropharyngeal, vaginal, vulvar, penile, anal, and rectal cancers.[1] Cervical and oropharyngeal are the two most common types of HPV-associated cancers, representing about 71% of all HPV-associated cancers in the US.[2] Nationally, cervical cancer rates are decreasing but oropharyngeal cancer rates are increasing.[3] While there are screening tests for cervical cancer, there are no routine screening tests for oropharyngeal cancer. However, primary prevention exists in the form of vaccines for HPV. Unfortunately, HPV vaccination rates remain low in Massachusetts, with 62.0% of teen (13-17 year old) girls and 51.4% of teen boys up-to-date (2 doses if immunocompetent and started vaccination before age 15, 3 doses if not immunocompetent or started vaccination after age 15) with the vaccination series in 2016.[4]

HPV vaccines have only been FDA approved since 2006. Due to the lag time between age at vaccination (11-12 years old) and average age at diagnosis for cervical (49 years old) or oropharyngeal cancer (62 among females, 59 among males), we are not yet able to directly examine how the vaccine has impacted cancer rates.[3] However, understanding trends of the two most common HPV-associated cancers is useful for state public health officials to inform cancer prevention, including vaccination promotion and policy efforts. Trends of cervical and oropharyngeal cancer incidence and mortality in Massachusetts have not been examined and the number of cancers potentially preventable by the HPV vaccine in Massachusetts is not known.

METHODS

In 2015, the estimated population of Massachusetts was 6.79 million people, of which 51.5% were female.[5] Only 15.4% of the population was 65 years old and over, while 20.4% was under 18 years old.[5] Most of the population was non-Hispanic white (73.5%), while 8.4% was

black, 11.2% was Hispanic, and 6.6% was Asian.[5] Due to legislation enacted in 2006, Massachusetts has a small percentage of people without health insurance (3.3% of those under age 65).[5]

The Massachusetts Cancer Registry (MCR) is part of the Massachusetts Department of Public Health (MDPH) and collects data on incident cancer cases in Massachusetts. The MCR has been collecting information since 1982 and the North American Association of Central Cancer Registries (NAACCR) has estimated that the MCR case ascertainment is more than 95% complete.[6] Information on new cases of cervical and oropharyngeal cancer diagnosed from 2004-2014 was obtained from the MCR. Oropharyngeal cancers included the following sites: base of tongue, tonsils, soft palate, and other parts of the oropharynx. All oropharyngeal cases were restricted to squamous cell carcinomas, and cervical cancer included squamous cell carcinomas and adenocarcinomas. The cancer death data were provided by the MDPH's Massachusetts Registry of Vital Records and Statistics (MRVRS). The MRVRS has legal responsibility for collecting reports of death on Massachusetts residents. We collected information on death from cervical cancer and oropharyngeal cancer from 2008-2014. Details on ICD codes included can be found in Appendix Table 1.1.

Incidence and mortality rates were age-standardized to the 2000 US population using 18 five-year age categories. We examined incidence and mortality rates by cancer site, gender, age group, and race/ethnicity. To assess trends we used joinpoint regression to calculate the annual percent change (APC) and perform hypothesis tests.[7] For cervical cancer, we also examined stage at diagnosis to supplement incidence information because of prevalent screening. Rates and trends were considered statistically significant if $p<0.05$. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NY).[8]

The MCR does not include information on the HPV genotype of the cancers. To estimate the number of cases attributable to an HPV infection, we used methods previously applied and published by the CDC's Morbidity and Mortality Weekly Report (MMWR) publication for the U.S.[2] We multiplied the percentage of cases that were HPV-positive from genotyping studies by the average annual number of cases.[1-2] The genotype prevalence data came from a national study that had data from seven cancer registries from varying times between 1993 and 2005.[1] They did not include any states from New England. We assumed the genotype prevalence from this study would be the same as the genotype prevalence in Massachusetts. We felt comfortable making this assumption due to similar a geographic prevalence in the national study, similar rates to smaller studies done in Massachusetts, and our assessment that this is the best data available to estimate HPV prevalence (Appendix Table 1.2).

About 30% of oropharyngeal cancers in the US are not related to HPV.[2] Risk factors for oropharyngeal cancer include smoking, alcohol, and the number of sexual and oral sex partners. Since we do not have information on the HPV status of the tumors in the MCR, we assessed trends in risk factors for oropharyngeal cancer to help us determine whether the potential burden of disease of these cancers in Massachusetts might be associated with HPV. To do this we used the Behavioral Risk Factor Surveillance System (BRFSS) Survey, which collects self-reported information on current cigarette smoking, heavy drinking, and binge drinking among adults in Massachusetts and the US from 1990-2010 using a random sample of land and cellular telephone numbers.[9] The number of sexual partners was collected from the Massachusetts BRFSS from 2000-2010. Per capita ethanol consumption data was collected from the National Institute on Alcohol Abuse and Alcoholism from 1977-2010.[10] It is important that teens are vaccinated for HPV before they begin any sexual activity. Additionally, we see that most HPV infections in the

US occur when people are in their 20s, so understanding teen sexual behaviors is important for prevention efforts.[11] Data on teen sexual behaviors including sexual intercourse with 4 or more partners and sexual intercourse before the age of 13 was collected by the Youth Risk Behavioral Surveillance System (YRBSS) for Massachusetts and the US sample from 1993-2015.[12] The YRBSS surveys are state- and nationally-representative surveys of high school youth, grades 9-12, that assess health risk behaviors.[12] We again used joinpoint regression to calculate the APC for trends in these risk factors over time.

RESULTS

Incidence rates by gender

From 2004 to 2014, 2,193 cases of cervical cancer and 3,996 cases of oropharyngeal cancer were diagnosed in Massachusetts (Table 1.1). The incidence rate of cervical cancer (5.46 cases per 100,000 females) was higher than the incidence rate of oropharyngeal cancer among males and females together (4.68 cases per 100,000). However, oropharyngeal is much more common in males and the incidence rate of oropharyngeal cancer among males is higher than the incidence rate of cervical cancer (7.85 vs 5.46 per 100,000 males and females respectively).

In Massachusetts, the incidence rate of cervical cancer has decreased by 2.41% annually ($p=0.004$), while the incidence rate of oropharyngeal cancer among males and females has increased by 3.01% annually from 2004 to 2014 ($p=0.0006$) (Figure 1.1). Among males, there was a 2.82% annual increase in the incidence rate of oropharyngeal cancer from 2004 to 2014 ($p=0.0002$). Females had a statistically significant increase in the rate of oropharyngeal cancer from 2004 to 2012 by 6.62% annually ($p=0.0007$), but then had a 13.73% decrease from 2012 to 2014 which was not statistically significant ($p=0.13$).

Table 1.1: Number and age-adjusted incidence (2004-2014) and mortality (2008-2014) rates[a] of cervical and oropharyngeal cancers in Massachusetts by sex, age, and race/ethnicity

	Cervical Cancer							
			Annual Percent Change				Annual Percent Change	
Characteristic	No. Cases	Incidence Rate	%	p value	No. Deaths	Mortality Rate	%	p value
Total	2,193	5.46	-2.41	0.004	374	1.29	-3.73	0.294
Age Group (Years)								
20-29	105	2.12	-6.40	0.073	-	-	-	
30-39	418	8.71	-3.93	0.027	16	0.54	17.36	0.145
40-49	545	9.76	-0.15	0.899	69	1.99	-10.93	0.211
50-59	453	8.74	-3.84	0.0002	94	2.75	08-10:30.61 10-14:-6.11	0.026 0.034
60-69	332	9.34	0.14	0.916	89	3.63	-11.93	0.025
70-79	188	8.24	-2.53	0.126	51	3.53	3.11	0.511
≥ 80	145	7.15	-4.01	0.084	49	3.77	-4.78	0.634
Race/Ethnicity								
White, Non-Hispanic	1,642	5.04	-2.54	0.020	305	1.25	-4.65	0.112
Black, Non-Hispanic	192	8.72	-4.74	0.038	34	2.28	-5.12	0.669
Asian	116	6.62	3.73	0.261	15	1.34	5.04	0.624
Hispanic	195	8.07	-6.36	0.010	20	1.41	4.07	0.868

	Oropharyngeal Cancer							
			Annual Percent Change				Annual Percent Change	
Characteristic	No. Cases	Incidence Rate	%	p value	No. Deaths	Mortality Rate	%	p value
Total	3,996	4.68	3.01	0.0006	820	1.46	-1.94	0.439
Sex								
Male	3,127	7.85	2.82	0.0002	586	2.35	-3.01	0.289
Female	869	1.91	04-12: 6.62 12-14:-13.73	0.0007 0.132	234	0.73	0.78	0.872
Age Group (Years)								
20-29	-	-	-		-	-	-	
30-39	48	0.51	1.81	0.701	-	-	-	
40-49	489	4.46	0.52	0.729	35	0.51	-2.44	0.836
50-59	1,378	13.70	1.37	0.144	177	2.72	-0.36	0.939
60-69	1,208	18.00	04-11: 9.85 11-14: -8.78	0.004 0.175	240	5.38	-3.79	0.197
70-79	622	15.41	6.06	0.001	195	7.54	-4.23	0.449
≥ 80	243	7.90	3.91	0.127	166	8.42	2.13	0.771
Race/Ethnicity								
White, Non-Hispanic	3,672	4.97	3.43	0.0005	733	1.50	-1.78	0.499
Black, Non-Hispanic	127	3.15	-0.61	0.823	46	1.83	-12.53	0.260
Asian	44	1.59	11.24	0.069	15	0.91	2.09	0.796
Hispanic	133	3.63	-0.67	0.883	23	1.09	20.68	0.313

[a]Per 100,000 person-years, standardized to the 2000 U.S. standard population, numbers may not add up due to unknown demographic, cells with fewer than 10 people not shown, multiple annual percent change values are shown when the regression indicated a statistically significant breakpoint

Figure 1.1: Trends in cervical and oropharyngeal cancer incidence (2004-2014) and mortality rates (2008-2014) in Massachusetts

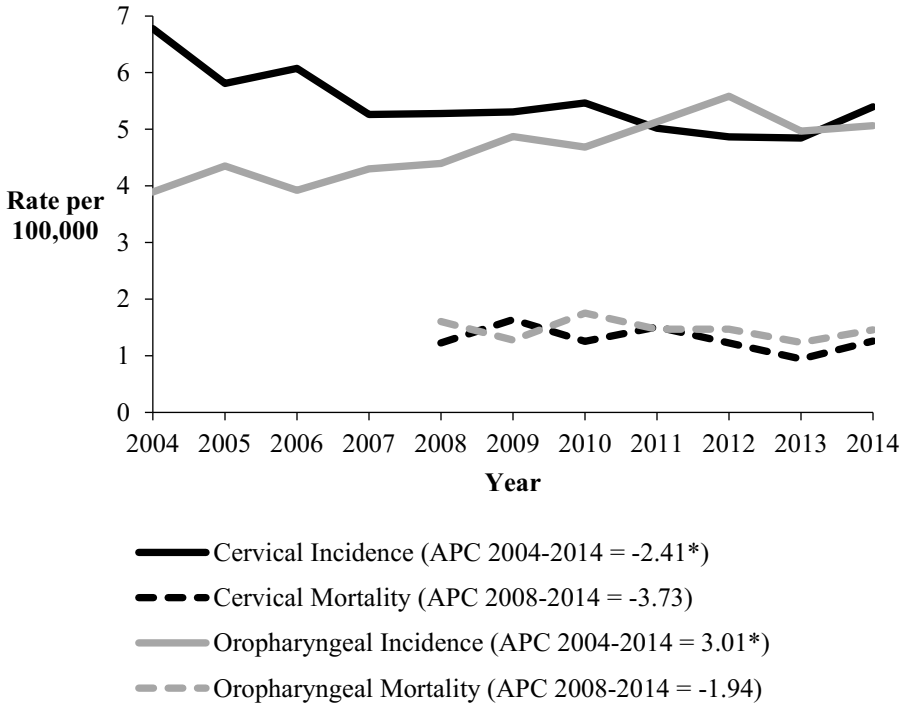

Figure 1.1: Rates are age-adjusted to the 2000 US standard population. The annual percent change (APC) values for the trends in incidence and mortality rates are presented in the legend. Statistically significant trend ($p<0.05$) in the APC are denoted with an *.

Incidence rates by age group

The average age at diagnosis for cervical cancer was 52.0 years old (standard deviation = 15.9, median=50, mode=45). For cervical cancer, incidence rates were the highest among females in their 40s (9.76 per 100,000) and 60s (9.34 per 100,000) (Table 1.1). Females of most ages experienced annual decreases in the incidence rate of cervical cancer, with the only statistically significant decreases occurring among females in their 30s (-3.93% APC, p=0.027) and 50s (-3.84% APC, p=0.0002). The average age at diagnosis for oropharyngeal cancer was 61.1 years old (standard deviation = 11.1, median=60, mode = 59). Oropharyngeal cancer had the highest incidence rate among people in their 60s (18.00 per 100,000) and 70s (15.41 per 100,000). Most age groups had annual increases in the incidence of oropharyngeal cancer, with

the only statistically significant increases observed among people in their 70s (6.06% APC, p=0.0001) from 2004-2014 and people in their 60s from 2004-2011 (9.85% APC, p=0.004).

Incidence rates by race/ethnicity

Non-Hispanic white females had lower incidence rates of cervical cancer than non-Hispanic black, Hispanic, and Asian females (5.04 vs 8.72, 8.07, and 6.62 per 100,000, respectively) (Table 1.1). For oropharyngeal cancer, non-Hispanic white people had higher incidence rates than non-Hispanic black, Hispanic, and Asian people (4.97 vs 3.15, 3.63, and 1.59 per 100,000, respectively). When we further examined stage at diagnosis for cervical cancer, Hispanic females were more likely to be diagnosed at stage I or II than all other race/ethnicities (Hispanic = 93.9%, Asian = 86.2%, non-Hispanic white = 83.4%, non-Hispanic black = 79.2%) (Appendix Table 1.3).

Trends in incidence rates for cervical and oropharyngeal cancer varied by race. Non-Hispanic white, non-Hispanic black, and Hispanic females had statistically significant annual decreases in the incidence rate of cervical cancer (-2.54% p=0.020, -4.74% p=0.038, and -6.36% p=0.010, respectively). However, the incidence rate of cervical cancer for Asian females increased by 3.73% annually, but this increase was not statistically significant (p=0.26). For oropharyngeal cancer, the incidence rate for non-Hispanic white people had statistically significant annual increases (3.43%, p=0.0005) and Asian people had a non-statistically significant annual increase (11.24%, p=0.069). Non-Hispanic black and Hispanic people had non-statistically significant annual decreases (-0.61% p=0.82, and -0.67% p=0.88, respectively).

Mortality rates by gender

From 2008 to 2014 there were 374 deaths from cervical cancer and 820 deaths from oropharyngeal cancer, of which 71% occurred in males (Table 1.1). The mortality rate from

oropharyngeal cancer among males (2.35 deaths per 100,000 males) was higher than the mortality rate from cervical cancer (1.29 deaths per 100,000 females) and oropharyngeal cancer among females (0.73 deaths per 100,000 females) (Figure 1.1). None of the trends in mortality from 2008 to 2014 in Massachusetts for cervical or oropharyngeal cancer were statistically significant. The annual mortality rate from cervical cancer decreased by 3.73% (p=0.29) and the annual mortality rate from oropharyngeal cancer decreased by 1.94% (p=0.44).

Mortality rates by age group

For both cervical and oropharyngeal cancers, the mortality rate increased with age. Women aged 80 and above had an age-specific mortality rate of 3.77 deaths per 100,000 for cervical cancer (Table 1.1). For oropharyngeal cancer, people aged 80 and above had an age-specific mortality rate of 8.42 deaths per 100,000. Women in their 50s had a statistically significant increase in the mortality rate of cervical cancer from 2008 to 2010 (30.61%, p=0.026) followed by a statistically significant decrease in mortality from 2010 to 2014 (-6.11%, p=0.034). Women in their 60s also experienced a statistically significant decrease in the mortality rate of cervical cancer from 2008 to 2014 (-11.93%, p=0.025). There were no statistically significant trends in the mortality rate of oropharyngeal cancer by age group.

Mortality rates by race/ethnicity

For both cervical and oropharyngeal cancers, non-Hispanic black people had a higher mortality rate than non-Hispanic white people (cervical: 2.28 vs 1.25 per 100,000, respectively; oropharyngeal: 1.83 vs 1.50 per 100,000, respectively) (Table 1.1). Non-Hispanic white and black people had non-statistically significant decreases in cervical (-4.65% p=0.11, and -5.12% p=0.67, respectively) and oropharyngeal cancer mortality (-1.78% p=0.50, and -12.53% p=0.26, respectively), while Asian and Hispanic people had non-statistically significant increases in

cervical (5.04% p=0.62, and 4.07% p=0.87, respectively) and oropharyngeal cancer mortality (2.09% p=0.80, and 20.68% p=0.31, respectively). However, these numbers were small and data should be interpreted with caution.

Number attributable to HPV

In Massachusetts, 180 cases (91%) of cervical cancer and 250 cases (70%) of oropharyngeal cancers were estimated to be attributable to infection with any type of HPV each year (Table 1.2). Of those cases estimated to be attributable to any type of HPV, 130 cases of cervical cancer (72%), and 220 cases of oropharyngeal cancer (88%) are estimated to be attributable to the two high risk types of HPV, HPV 16 and 18, which are targeted by all available HPV vaccines. Of those cases estimated to be attributable to any type of HPV, 160 cases of cervical cancer (89%) and 240 cases of oropharyngeal cancer (96%) are estimated to be attributable to HPV 16, 18, 31, 33, 45, 52, and 58, which are targeted by the new 9-valent vaccine.

Oropharyngeal cancer risk factors

There are many risk factors for oropharyngeal cancer including tobacco, alcohol, and HPV-associated risk factors such as the number of sexual partners. In Massachusetts, 14% of

Table 1.2: Estimated annual average number of cancers attributable to HPV for cervical and oropharyngeal cancer in Massachusetts from 2004 to 2014

Cancer	Average Annual Number	Estimated attributable to any HPV type Number (%)	Estimated attributable to HPV 16/18 Number (%)	Estimated attributable to HPV 16/18/31/33/45/52/58 Number (%)
Cervical	199	180 (90.6)	130 (66.2)	160 (80.9)
Oropharyngeal	363	250 (70.1)	220 (60.2)	240 (65.9)
Males	284	210 (72.4)	180 (63.4)	190 (67.8)
Females	79	50 (63.3)	40 (50.8)	50 (60.3)

Number estimated to be attributable to HPV is rounded to the nearest 10, percentages from source [1], average annual number is total from 2004-2014 divided by 11

adults reported current cigarette smoking in 2010. The percentage of adults smoking decreased from 1990 to 2006 by 1.88% annually and then decreased from 2006 to 2010 by 5.56% annually ($p<0.0001$ and $p<0.0001$, respectively) (Appendix Figure 1.1a). Massachusetts had a per capita annual ethanol consumption of 2.50 gallons in 2010 (Appendix Figure 1.1b). The consumption decreased from 1977 to about 1992 and then remained more constant. The prevalence of heavy drinking was 7.2% in 2015, with 17.7% reporting binge drinking. Among Massachusetts adults ages 18 to 64 who reported being sexually active in 2010, 92.7% reported having 1 partner, 5.4% reported having 2-3 partners, and 1.9% reported 4+ partners. From 2000-2010, there was a 5.32% decrease in the percentage of adults having sex with 2-3 partners ($p=0.015$) and a 2.21% decrease in the percentage of adults having 4+ partners ($p=0.38$). For teen sexual behaviors in Massachusetts, there was a statistically significant decrease in the percentage of high school students ever having sex with four or more partners from 1993-2003 (-3.3% annually, $p=0.009$) and 2009-2013 (-8.2% annually, $p=0.02$) (Appendix Figure 1.2a), and a statistically significant decrease in the percentage of high school students having sex before age 13 from 1993-2001 (-6.4% annually, $p=0.008$) and 2007-2015 (-9.2% annually, $p=0.005$) (Appendix Figure 1.2b).

DISCUSSION

In Massachusetts, the incidence rates of the two most common HPV-associated cancers are moving in opposite directions. The incidence rate of oropharyngeal cancer has been increasing while the incidence rate of cervical cancer has been decreasing. Recent reports on oropharyngeal cancer in the US project that the prevalence of oropharyngeal cancer will pass the prevalence of cervical cancer by 2020.[13] In Massachusetts this has already happened; the number of cases of oropharyngeal cancer is greater than the number of cases of cervical cancer (363 vs 199 on average each year) and the incidence rate of oropharyngeal cancer among males is

already higher than the incidence rate of cervical cancer among females (7.85 vs 5.46 per 100,000). Reasons for the early crossing of incidence rates for cervical and oropharyngeal cancer should be explored further.

Cervical cancer screening may have caused the decreasing incidence rate of cervical cancer in Massachusetts and the US. Massachusetts has a lower rate of cervical cancer incidence and mortality than the US (incidence: 5.2 vs 7.4 per 100,000 for 2008-2012; mortality: 1.3 vs 2.3 per 100,000 for 2009-2013).[2,14] While Massachusetts saw a 2.4% decrease in the incidence rate and a 3.7% decrease in the mortality rate of cervical cancer from 2004-2014, nationally there was 12.7% decrease in the incidence rate of cervical cancer from 1990-2006 followed by a 0.4% decrease from 2006-2014, and a 0.7% decrease in mortality from 2004 to 2014.[15] Screening for cervical cancer, using cytology with or without HPV cotesting, is widely available but there are no routine screening tests for oropharyngeal cancer. Massachusetts has a small percentage of the population without health insurance as health insurance has been mandatory since 2006. In 2014, 88.0% of females ages 21-65 reported having a Pap smear in the last 3 years in Massachusetts compared to the US median of 82.6%.[9] In addition to the higher screening prevalence, vastly fewer females in Massachusetts were diagnosed at a distant stage when compared to the US (3% in Massachusetts vs 14% nationally) and the mortality rate from cervical cancer was lower in Massachusetts than the US.[14] If anything, the high screening rate for cervical cancer in Massachusetts should result in a higher incidence of early stage cancers if screening tests are catching slow growing non-symptomatic cases. However, cervical cancer screening also detects pre-cancerous lesions which can be removed before they become cancerous. The lower incidence, coupled with relatively lower mortality suggests that the true incidence of cervical cancer among women in Massachusetts is lower than that of the general US population.

However, due to the prevalence of screening tests and more recently the HPV vaccine, cervical cancer should be almost completely preventable. Further research is needed to understand why the rate of cervical cancer is still so high in Massachusetts. This may be due to problems accessing care after positive screening tests and a lack of education about screening tests and vaccination, particularly among black women who have the greatest disparities in incidence and mortality. However, it is of note that the rates for black women have been decreasing in the US from 1990 to 2014.[16] Also of note, there appears to be an increasing incidence and mortality for cervical cancer among Asian women. This trend requires further monitoring as future data becomes available and additional research to understand the reason for this increase.

The increase in oropharyngeal cancers nationally is thought to be due to a rise in HPV-positive cancers while HPV-negative cancers have been decreasing.[17] HPV-negative oropharyngeal cancers are associated with heavy tobacco and alcohol use.[17] Massachusetts had a higher incidence rate of oropharyngeal cancer than that in the US (5.0 vs 4.5 per 100,000 for 2008-2012).[2] The incidence rate of oropharyngeal cancer in Massachusetts increased by 2.8% annually from 2004-2014, while the incidence rate of oropharyngeal cancer in the US increased by 3.1% annually from 1999-2014.[15] Massachusetts had a slightly higher per capita ethanol consumption than the US (2.50 vs 2.26 gallons in 2010), as well as a higher prevalence of heavy drinking (7.2% vs 5.9%) and binge drinking (17.7% vs 16.3%) in 2015.[9-10] However, Massachusetts had a lower prevalence of current smoking than the US with 14.0% current smokers in Massachusetts compared to 17.5% of the US in 2010.[9] Yet, looking at the trends of smoking and alcohol consumption over time (Appendix Figure 1.2), these behaviors have been decreasing in both the US and Massachusetts which makes it unlikely that they account for the

recent increases in oropharyngeal cancer incidence. The higher alcohol intake in Massachusetts may explain why Massachusetts has a higher incidence rate of oropharyngeal cancer than the US, but information on the HPV status of the cancers is needed.

The HPV-positive oropharyngeal cancers tend to be diagnosed in younger males who are non-smokers and have a better prognosis than HPV-negative cancers.[17] In Massachusetts, there was an increasing incidence rate for all age groups, with statistically significant increases for people in their 70s from 2004-2014 and 60s from 2004-2011. Unlike the trends at the national level, there was no statistically significant increase in middle-aged males in Massachusetts, potentially reflecting more HPV-negative cases in Massachusetts. However, the somewhat decreasing mortality rate is in line with the better prognosis of the HPV-positive cases. Risk factors for the HPV-positive oropharyngeal cancers include an increased number of sexual or oral sexual partners.[17] Unfortunately, long-term data on oral sex in Massachusetts are unavailable. Nationally, more males and females engaged in oral sex in the 2009 National Survey of Sexual Health and Behavior study than the 1992 National Health and Social Life Survey.[18] The 2009 National Survey of Sexual Health and Behavior study found that most adults have engaged in oral sex, with over half of women and men age 18 to 49 receiving oral sex in the past year.[18] The increase in the number of oral sex partners may be why there is an increase in the rates of oropharyngeal cancer; however, further research is needed to understand the risk factors for HPV-positive oropharyngeal cancers.

The rise in the incidence rate of oropharyngeal cancer, especially among males, and the declines in traditional risk factors, highlights the need to improve HPV vaccination coverage. While we are not yet able to see the impact of HPV vaccination on cancer incidence rates, understanding these trends sends a strong message about the need for prevention. It is estimated

that of the cases that are thought to be caused by HPV, up to 89% of cervical cancers and 96% of oropharyngeal cancers may be caused by a strain of HPV currently covered by the vaccine. Massachusetts has a higher vaccination rate than the US average, but improvements are needed. In 2016, 78% of girls and 66% of boys in Massachusetts had at least one dose compared with 65% of girls and 56% of boys nationally.[4] However, the percentage completing the vaccine series is even lower, especially among boys. The recommendation of the Advisory Committee on Immunization Practices for a two dose HPV vaccine series, for adolescents who do not have certain immunocompromising conditions and begin vaccination before age 15, will provide an opportunity to improve immunization coverage and achieve protection against vaccine-preventable HPV-related cancers.[19]

In addition, better vaccination coverage is needed as teens in Massachusetts continue to be sexually active. In Massachusetts, the percentage of high school students reporting having sex did not change from 2003 to 2013.[20] While the percentage of students having sex with four or more partners and the percentage of students having sex before age 13 decreased from 1993 to 2015, the need for HPV vaccination before the start of sexual activity and sexual education regarding HPV and other sexually transmitted infections remains important (Appendix Figure 1.2).[12]

This study contains some limitations that should be considered when interpreting the findings. Data on cancer incidence may be under-reported in areas of Massachusetts close to neighboring states. However, the MCR has a reciprocal reporting agreement with 41 states, which should help reduce the problem of under-reporting. When data are analyzed by cancer site and another characteristic small numbers reduce precision; as a result, differences in sub group rates may be due to chance. The MCR does not contain information on whether HPV DNA is

present in cancer tissues so the proportion attributable to HPV is assumed to be the same as the results of a genotyping study.[1] While the assumptions made to apply these data were stated in the methods and Appendix Table 1.2, we can see that our study has fewer non-Hispanic black cases, more male cases, and more cases diagnosed at an older age (age 70+) than the genotype paper.[1] Non-Hispanic blacks tend to have a lower prevalence of HPV than non-Hispanic whites, so this would lead our estimates to be too low.[1] People diagnosed at an older age tend to have a lower HPV prevalence so this would lead our estimate to be too high.[1] Many studies of oropharyngeal cancer in Massachusetts show lower prevalence of HPV positive cases than the national studies.[21-25] However, these studies tend to be smaller, may represent people treated in Boston rather than people who live in Massachusetts, and tend to not be population-based. If the HPV positive prevalence in Massachusetts is truly lower than the national study, then our numbers attributable are over-estimates. Lastly, we did not adjust for hysterectomy prevalence when calculating rates of cervical cancer. From the data available in the Massachusetts BRFSS, we were not able to get the prevalence of hysterectomies by age and race for 2004-2014. Additionally, there was a change in BRFSS methodology in 2011 that precluded combining data from before and after 2011. A different study using MCR data and modeling hysterectomy prevalence shows that adjusting for hysterectomies increases the rate of cervical cancer.[26] Thus cervical cancer rates presented in this analysis are likely underestimates of the corrected rates, due to a population denominator that is too large since women with hysterectomies have not been removed, and depending on the trends in hysterectomy by race/ethnicity may underestimate the level of disparity in cervical cancer incidence and mortality.

Massachusetts has a strong public health program working on HPV vaccination and HPV-associated cancers. The MDPH Comprehensive Cancer Control and Prevention Network

has developed a plan which includes evidence-based strategies for both decreasing the number of HPV-associated cancers and improving HPV immunization coverage in both males and females.[27] In addition, the Cervical Cancer Working Group, Oral HPV Prevention Task Force, and other MDPH program partners have an integrated multidisciplinary approach to education, immunization, screening and care, and are dedicated to the reduction of HPV-associated cancer in Massachusetts.[28] Historical reports of cancers in Massachusetts can be found on the Massachusetts Cancer Registry website through the statewide and special reports.[29]

In Massachusetts, while the incidence rate of oropharyngeal cancer has been rising among males and is higher than the rate in the US, the incidence rate of cervical cancer has been decreasing among females and is lower than the rate in the US. These findings are useful to state public health departments to support the promotion of HPV vaccination among both girls and boys. It also supports patient and provider efforts to promote cancer prevention, especially for HPV-associated cancers.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Appendix Table 1.1: ICD codes

	ICD-O-3		ICD-10 cause of death	
Cancer	**Code**	**Definition**	**Code**	**Definition**
Cervical	C53.0	Endocervix	C53.0	Endocervix
	C53.1	Exocervix	C53.1	Exocervix
	C53.8	Overlapping lesion of cervix uteri	C53.8	Overlapping lesion of cervix uteri
	C53.9	Cervix uteri	C53.9	Cervix uteri
Oropharyngeal	C01.9	Base of tongue, NOS	C01	Base of tongue
	C02.4	Lingual tonsil	C02.4	Lingual tonsil
	C02.8	Overlapping lesion of tongue	C02.8	Overlapping lesion of tongue
			C02.9	Tongue, unspecified
	C05.1	Soft palate, NOS	C05.1	Soft palate
	C05.2	Uvula	C05.2	Uvula
	C09.0	Tonsillar fossa	C09.0	Tonsil fossa
	C09.1	Tonsillar pillar	C09.1	Tonsillar pillar
	C09.8	Overlapping lesion of tonsil	C09.8	Overlapping lesion of tonsil
	C09.9	Tonsil, NOS	C09.9	Tonsil, unspecified
	C10.0	Vallecula	C10.0	Vallecula
	C10.1	Anterior surface of epiglottis	C10.1	Anterior surface of epiglottis
	C10.2	Lateral wall of oropharynx	C10.2	Lateral wall of oropharynx
	C10.3	Posterior wall of oropharynx	C10.3	Posterior wall of oropharynx
	C10.4	Brachial cleft	C10.4	Brachial cleft
	C10.8	Overlapping lesion or oropharynx	C10.8	Overlapping lesion or oropharynx
	C10.9	Oropharynx, NOS	C10.9	Oropharynx, unspecified
	C14.0	Pharynx, NOS	C14.0	Pharynx, unspecified
	C14.2	Waldeyer's ring	C14.2	Waldeyer's ring
	C14.8	Overlapping lesion of lip, oral cavity and pharynx	C14.8	Overlapping lesion of lip, oral cavity and pharynx

Appendix Table 1.2: Details on genotyping study used to estimate HPV prevalence for the cancers and related studies from Massachusetts

Paper (Year)	Study Type and Number of Cases	Geographic Area	Years Incident Cases Collected	Prevalence HPV + Cases		Findings/Use/Limitations
				Cervical	Oropharyngeal	
Genotyping Data Nationally						
Sarayia et al (2015)[1]	Cross-sectional study of select US cancer registries, 777 cervical cases, 588 oropharyngeal cases	Los Angeles, Hawaii, Iowa, Kentucky, Florida, Louisiana, Michigan	1993-2005 1 registry 1993-1999 1 registry 2000-2004 1 registry 1994-2004 4 registries 2004-2005	90.6%	70.1%	Used for HPV + prevalence in our estimates
Steinau et al (2014)[appendix source 2]	Cross-sectional study of select US cancer registries, 557 oropharyngeal cases	Los Angeles, Hawaii, Iowa, Kentucky, Florida, Louisiana, Michigan	1995-2005 1 registry 1995-1999 1 registry 2000-2004 1 registry 1994-2004 4 registries 2004-2005	NA	72.4%	High-risk HPV prevalence by registry: Los Angeles = 17 cases (85.0%) Hawaii = 33 cases (84.6%) Iowa = 4 cases (30.7%) Kentucky = 74 cases (63.8%) Florida = 101 cases (72.1%) Louisiana = 75 cases (78.9%) Michigan = 92 cases (68.6%)
Genotyping Data in Massachusetts						
Wright et al (2013)[appendix source 3]	Chart review, Brigham and Women's Hospital, 80 cervical cases	Boston for treatment	2005-2011	96.3%	NA	To compare MA prevalence to national prevalence
Addison et al (2017)[19]	Case series from Massachusetts General Hospital, 235 oropharynx cases	Boston for treatment	2002-2012	NA	64.7%	To compare MA prevalence to national prevalence Eligible patients had to be undergoing radiation
Lorch et al (2015)[20]	Chart review, Dana Farber Cancer Institute, 500 oropharyngeal cases	Boston for treatment	2001-2011	NA	43% HPV + 44% unknown status	To compare MA prevalence to national prevalence Eligible patients had to be stage III or IV

Appendix Table 1.2 (Continued): Details on genotyping study used to estimate HPV prevalence for the cancers and related studies from Massachusetts

Paper (Year)	Study Type and Number of Cases	Geographic Area	Years Incident Cases Collected	Prevalence HPV + Cases		Findings/Use/Limitations
				Cervical	Oropharyngeal	
Genotyping Data in Massachusetts						
Nelson et al (2017)[21]	Population-based greater Boston area, 486 pharyngeal cases	Greater Boston area	1999-2003 and 2006-2011	NA	60.7%	To compare MA prevalence to national prevalence
Nichols et al (2010)[22]	Case series from Partners Healthcare System, 68 oropharynx cases	Massachusetts	1996-2006	NA	78% HPV 16	To compare MA prevalence to national prevalence Eligible patients had to be undergoing chemoradiation
Ringstrom et al (2002)[23]	Case series from Dana-Farber, 29 oropharynx cases	Boston for treatment	1994-1998	NA	52% HPV 16 oropharynx 64% HPV 16 tonsil	To compare MA prevalence to national prevalence

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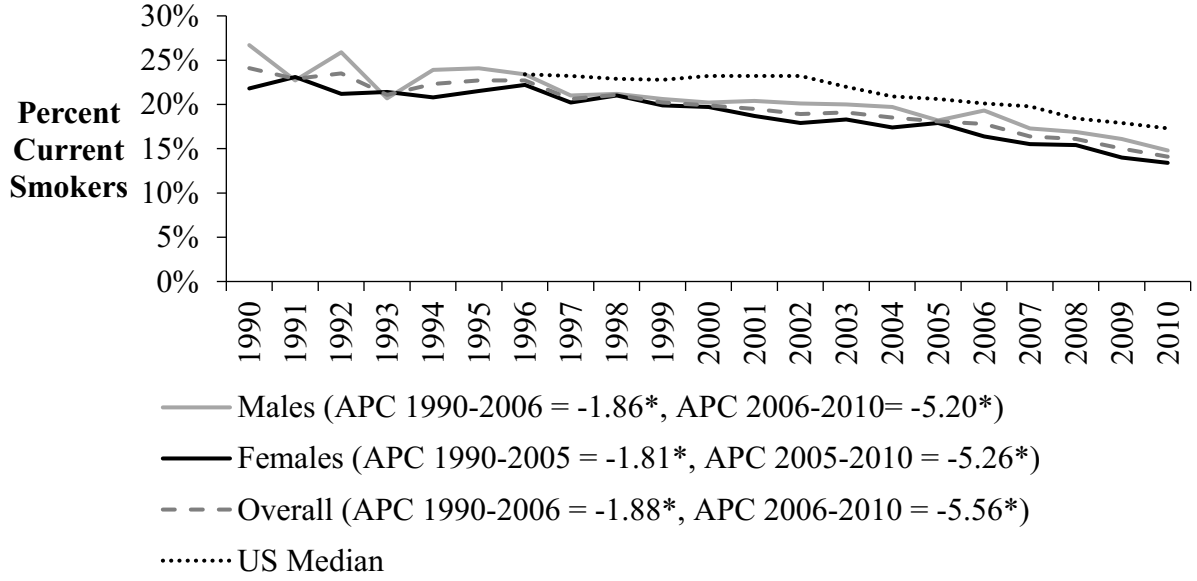
Appendix Table 1.3: Cervical cancer stage at diagnosis by age and race/ethnicity in Massachusetts, 2004-2014

	Stage I Number (%)	Stage II Number (%)	Stage III Number (%)	Stage IV Number (%)
Total	1,075 (50.1)	729 (34.0)	284 (13.2)	57 (2.7)
Age Group (Years)				
20-29	76 (72.4)	23 (21.9)	-	-
30-39	295 (70.6)	100 (23.9)	16 (3.8)	-
40-49	328 (60.2)	157 (28.8)	49 (9.0)	11 (2.0)
50-59	198 (43.7)	174 (38.4)	72 (15.9)	-
60-69	112 (33.7)	143 (43.1)	71 (21.4)	-
70-79	54 (28.7)	78 (41.5)	43 (22.9)	13 (6.9)
≥ 80	35 (24.1)	63 (43.5)	34 (23.5)	13 (9.0)
Race/Ethnicity				
White, Non-Hispanic	817 (49.8)	552 (33.6)	232 (14.1)	41 (2.5)
Black, Non-Hispanic	86 (44.8)	66 (34.4)	30 (15.6)	10 (5.2)
Asian	62 (53.5.1)	38 (32.8.6)	13 (11.2)	-
Hispanic	110 (56.4)	73 (37.4)	-	-

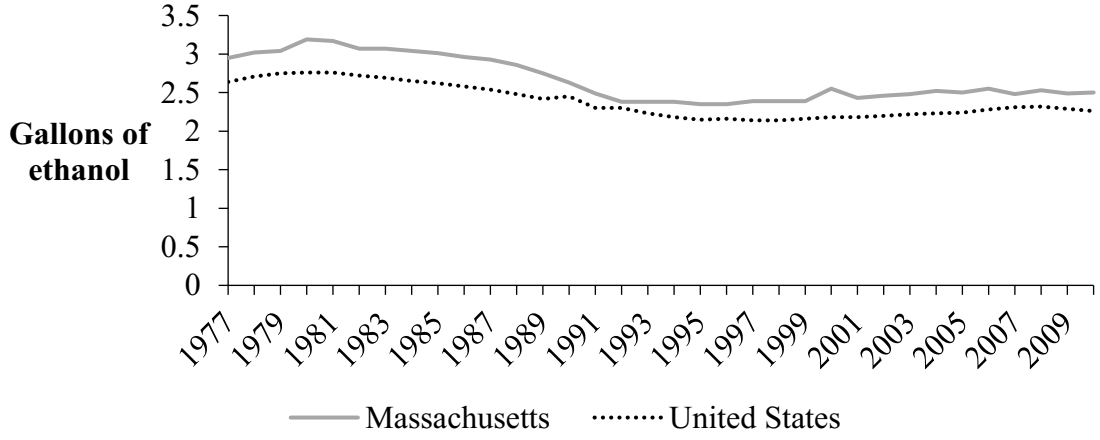
Cells with counts under 10 people are not shown, SEER summary stages are presented, percentages are the percent of total cases with that stage for the subgroup provided in each row, numbers may not add up due rounding and missing race/ethnicity values

Appendix Figure 1.1: Trends in traditional risk factors for oropharyngeal cancer in Massachusetts compared to the United States

Appendix Figure 1.1a: Trends in current cigarette smoking among Massachusetts adults from 1990-2010 by gender compared to the United States Median (1996-2010) from the BRFSS[9]



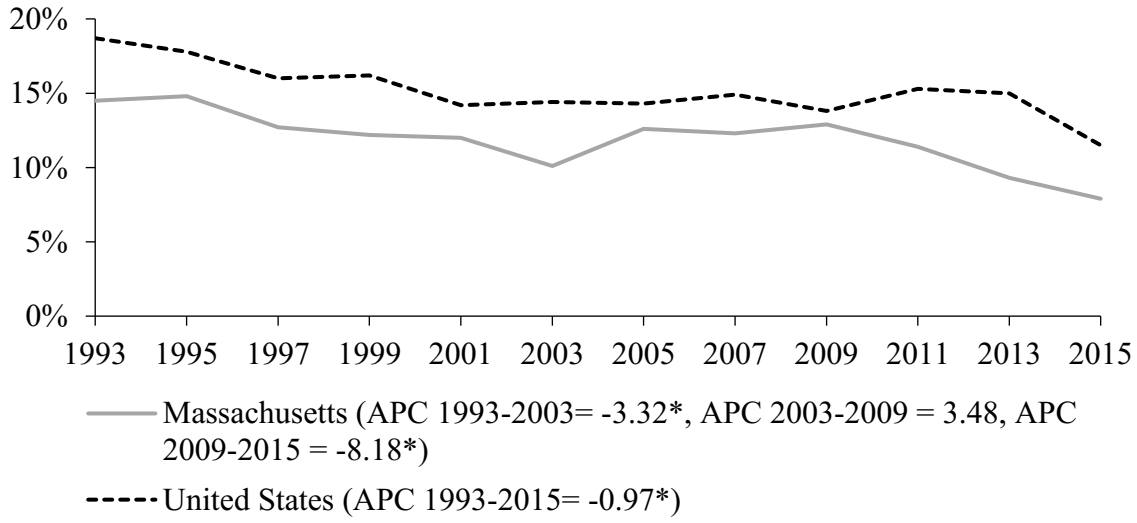
Appendix Figure 1.1b: Trends in per capita ethanol consumption in Massachusetts and the United States from 1977-2010 among people age 14 and older from NIAAA[10]



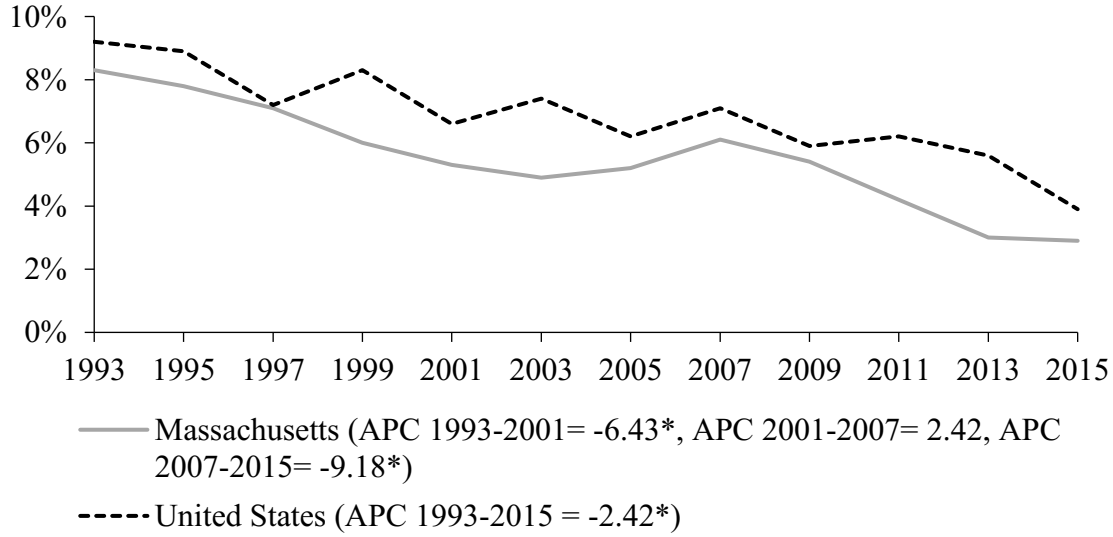
Appendix Figure 1.1: The current cigarette smoking prevalence is shown for Massachusetts males, females, and the entire population of Massachusetts from 1990 to 2010 in comparison to the median prevalence in the United States from 1996 to 2010 in Figure 1.1a. The per capita ethanol consumption for Massachusetts and the United States from 1977 to 2010 is shown in Figure 1.1b. The annual percent change values for the trends are presented in the legend. For figures 1.1a and 1.1b, statistically significant trends ($p<0.05$) in the APC are denoted with an *.

Appendix Figure 1.2: Trends in HPV-associated oral cancer risk factors among high school students from the YRBSS[12]

Appendix Figure 1.2a: Percent of US high school students reporting ever having sexual intercourse with 4 or More Persons, 1993-2015



Appendix Figure 1.2b: Percent of high school students reporting having sexual intercourse before age 13, 1993-2015



Appendix Figure 1.2: The prevalence of high school students having sex with 4 or more persons in Massachusetts and the United States is shown in Figure 1.2a. The prevalence of high school students having sex before age 13 in Massachusetts and the United States is shown in Figure 1.2b. The annual percent change values for the trends are presented in the legend. For figures 1.2a and 1.2b, statistically significant trends ($p<0.05$) in the APC are denoted with an *.

Effect of Legislation to Increase Uptake of Human Papillomavirus Vaccination on Adolescent Sexual Behaviors

Erin E. Cook, MPH; Atheendar S. Venkataramani, MD, PhD; Jane J. Kim, PhD; Rulla M. Tamimi, ScD; Michelle D. Holmes, MPH, MD, DrPH.

ABSTRACT

Background: Despite preventative health benefits of the human papillomavirus (HPV) vaccination, uptake in the United States remains low. Twenty-four states have enacted legislation regarding HPV vaccination and education. One reason these policies have been controversial is due to concerns that they encourage risky adolescent sexual behaviors. The aim of this study is to determine if state HPV legislation is associated with changes in adolescent sexual behaviors.

Methods: This is a difference-in-difference study using data on adolescent sexual behaviors from the school-based state Youth Risk Behavior Surveillance System (YRBSS) from 2001-2015. Sexual behaviors included ever having sexual intercourse in the last three months and condom use during last sexual intercourse. We compared changes in sexual behaviors among high school students before and after HPV legislation to changes among high school students in states without legislation.

Results: 715,338 participants reported ever having sexual intercourse in the last 3 months and 217,077 sexually active participants reported recent condom use. We found no substantive or statistically significant associations between HPV legislation and adolescent sexual behaviors. Recent sexual intercourse decreased by 0.90 percentage points (p=0.21) and recent condom use increased by 0.96 percentage points (p=0.32) among adolescents in states that enacted legislation compared to states that did not. Results were robust to a number of sensitivity analyses.

Conclusion: Implementation of HPV legislation was not associated with changes in adolescent sexual behaviors in the United States. Concern that legislation will increase risky adolescent sexual behaviors should not be used when deciding to pass HPV legislation.

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States.[1] Persistent infection with a high risk strain can lead to serious health problems including cervical, anal, penile, vaginal, vulvar, and oropharyngeal cancers, as well as genital warts in both men and women.[2] Currently, there are three Food and Drug Administration (FDA) approved HPV vaccines, for which multiple doses are recommended.[3-5] The Centers for Disease Control and Prevention (CDC) has recommended routine HPV vaccination for girls ages 11-12 since 2006 and boys ages 11-12 since 2009, with catch-up vaccination for older adolescents and young adults.[6,7] However, despite the availability of the vaccines, uptake remains low, with only 49.5% of girls and 37.5% of boys having up-to-date HPV vaccinations in 2016.[8]

Many reasons for the low uptake of the HPV vaccine have been proposed, including high costs and poor access; difficulty completing the multi-dose regimen; safety and health concerns; and worries that the vaccine will promote unsafe sexual activity among adolescents.[9-12] Currently 23 states and the District of Columbia (DC) have successfully passed legislation regarding HPV to help improve HPV vaccination coverage.[13] These policies vary in terms of leniency and include: requiring schools to provide information about HPV vaccination to students; subsidizing costs and incentivizing insurers to cover the vaccine; and mandating vaccination (Supplemental Table 1).[13] Further adoption of these policies has been hampered by a number of concerns.[13,14] One concern is that encouraging adoption of the HPV vaccination may encourage risky sexual behaviors among adolescents, and it may be seen as conflicting with abstinence only sexual education.[14-17] Consequently, many states have had to defer vaccination mandates, and instead pass related legislation focusing on HPV education or cost.[17,18] While recent research has found no changes in sexually transmitted infections (STIs) among privately-insured individuals

receiving the HPV vaccine, the broader impacts of policies to increase vaccine uptake on sexual behaviors in the general adolescent population have not been examined.[19] Rigorous evidence in this domain will be critical as policymakers continue to grapple with strategies to raise vaccination rates.

In this study, we examined the impact of state-level legislation aiming to raise awareness and uptake of the HPV vaccination on adolescent sexual behaviors. We used a quasi-experimental, difference-in-difference approach to assess how the policy is associated with the number of sexual partners and condom use during last sexual intercourse.[20]

METHODS

Data on the outcomes of adolescent sexual behaviors were collected from the 2001-2015 state Youth Risk Behavior Surveillance System (YRBSS).[21] The state YRBSS is a large, state representative, biannual, school-based survey of 9th to 12th grade students from the United States. Under-represented minorities were purposely over sampled at each stage of the three-stage sampling procedure.[22] The state YRBSS survey collected information from students in 25 states without HPV legislation and 16 states with HPV legislation (Supplemental Table 2.1). States could choose when they wanted to publicly report their results so the coverage of states differed each year during our study period.

The YRBSS asked students to report if they ever had sexual intercourse in the last 3 months and if they used a condom the last time they had sexual intercourse. Ever having sexual intercourse during the last 3 months was a binary yes/no variable (0 for people who never had sex or did not have sex in the last 3 months, 1 for people who had sex during the last 3 months). Condom use during last sexual intercourse is a binary yes/no variable that is conditional on ever having had sex in the last 3 months. As a secondary outcome we looked at the number of sexual

partners during the last 3 months as a continuous variable from 0 (people who never had sex or did not have sex in last 3 months) to 6 (6 or more partners in the last 3 months).

The main exposure was whether respondents' state of residence had legislation aiming to raise HPV vaccination rates in place during the year of the interview. Information on the type of policy and year of passage was obtained from the National Conference of State Legislatures (Supplemental Table 2.1).[23] The exposure was then further categorized by the type of legislation that was passed: vaccination mandates, HPV education (in schools, for parents, general awareness, research funds), and vaccine cost and accessibility (cost of vaccine, insurance coverage, prescription requirements).

We used difference-in-difference models to study the association of the legislation with adolescent sexual behaviors.[20] We compared changes in sexual behavior for adolescents living in states that passed HPV legislation before and after policy implementation against the same changes in states that did not pass legislation. In our model we adjusted for respondent age, gender, race, and grade. To adjust for potential confounders for the association between the states with legislation and adolescent sexual health behaviors, we added state-year factors to the model including state-specific linear time trends. Our models include state effects that account for any fixed differences between states (such as political, educational, or teen pregnancy differences) and the models also include year effects that account for any trends in the risky teen sexual behaviors over time that are similar across all states. As a secondary analysis, we also adjusted for rates of unemployment, teen pregnancies, and sexually transmitted diseases among teens ages 15-19, as well as the Children's Health Insurance Program (CHIP) and the Medicaid program of the states, the majority political party of the state legislature and the political party of the governor. CHIP and Medicaid was included in case any changes to health care coverage for

adolescents or vaccinations occurred around the same time that legislation was passed, and could be acting as a confounder for the relationship between legislation and adolescent sexual behaviors. We estimated models defining the exposure as passage of any policy as well as passage of specific types of legislation including mandates, legislation about vaccine cost or access, and legislation about education. Due to the small number of states with mandates and the timing of the mandates we were not able to examine the effect of the mandates separately and instead, they are only included in the any policy analysis.

Even though our main outcomes were binary variables we used ordinary least squares regression to estimate our models. This is because there are well known biases in limited dependent variable estimators in fixed effect models.[24] For all models, we corrected standard errors for clustering at the state level to account for serial correlation in the outcome.[25] Survey weights were used when examining the descriptive characteristics of states with legislation compared to states without legislation. Survey weights were not used in the difference-in-difference models because individual-level error terms clustered within a larger group (each state) could yield inappropriately inflated standard errors.[26] Additionally, we did not *a priori* expect large heterogeneous effects since the survey was not sampled by the outcome of interest.[26] However, we still ran the main models using the survey weights to compare with our main models that did not include survey weights.

We estimated several additional models. First, we assessed potential violations of the parallel trends assumption of the difference-in-difference model.[20] Specifically, we examined whether trends in sexual behavior prior to policy implementation differed in states passing policies versus those that did not. Second, we estimated our main models by subgroups of age, gender, grade, and race/ethnicity. Bonferroni corrections were used to account for multiple

testing. With 18 main regressions run for the analysis, results were considered statistically significant when the p value <0.003. Third, since an assumption of this model is that the effects are immediate we did a lagged analysis to see what happened when we looked at the effect of the legislation among students, years after it was passed. The idea of the lag is that most HPV vaccination education and coverage should be affecting 11-12 year-olds and our YRBSS data is taken from older students (mainly 15-18 year-olds), so looking at a lagged timing of legislation will let us see if the effect of the legislation was limited to kids who were age 11-12 at the time of the legislation. Additionally, the lagged analysis also accounts for the fact that implementation of the legislation most often happened the year after the policy was passed. However, since states did not always report their data for every survey year we do not have as many states reporting their data after 2011, and lagged results should be interpreted with caution. Fourth, as a pre-specified falsification test, we also examined lead effects since the first HPV vaccine was approved in 2006.[27] This study is exempt from human subjects review by IRB given the use of publicly-available, de-identified data.

RESULTS

From 2001 to 2015, 886,981 high school students participated in the state YRBSS surveys. Of those respondents, 224,177 (25.3%) reported having sexual intercourse in the last 3 months, 491,161 (55.4%) reported that they did not have sexual intercourse in the last 3 months, and 171,643 (19.4%) did not respond to that question. 715,338 high school students reported the number of sexual partners during the last three months (80.6% of all students participating) and 217,077 high school students who ever had sexual intercourse in the last 3 months reported condom use during last sexual intercourse in the YRBSS (96.8% of students who reported having sexual intercourse in the last 3 months. Students in states with HPV legislation were

Table 2.1: Characteristics of students in states with HPV legislation and states without HPV legislation overall and by pre-legislation and post-legislation time periods

	2001-2015	2001-2005		2007-2015	
	All states (n=886,981) Percent	No Legislation (n=122,164) Percent	HPV Legislation (n=95,728) Percent	No Legislation (n=282,363) Percent	HPV Legislation (n=386,726) Percent
Age					
14 or younger	11.1	9.7	11.7	10.4	11.9
15	25.7	26.3	26.5	25.2	25.6
16	25.8	26.2	25.7	25.8	25.7
17	23.3	22.7	22.3	23.9	23.3
18	14.2	15.1	13.9	14.8	13.4
Gender					
Male	50.8	50.8	50.7	50.9	50.8
Female	49.2	49.3	49.3	49.2	49.2
Grade					
9	28.7	30.4	30.2	27.8	28.2
10	25.8	25.8	26.0	25.9	25.8
11	23.5	23.0	22.9	23.8	23.6
12	22.0	20.9	20.9	22.5	22.5
Race					
White	58.4	65.7	63.4	56.9	55.0
Black/Hispanic/ Other	41.6	34.3	36.6	43.1	45.0
Smoking in last 3 months					
Yes	17.5	22.6	22.5	15.8	15.3
No	82.5	77.4	77.5	84.2	84.7
Alcohol use in last 3 months					
Yes	38.5	43.5	43.8	35.6	36.8
No	61.5	56.5	56.2	64.4	63.2
Taught about AIDS in school					
Yes	90.1	91.9	91.8	89.3	89.1
No	9.9	8.1	8.2	10.7	10.9
Condom use during last sexual intercourse					
Yes	60.8	63.0	62.8	60.0	59.8
No	39.2	37.0	37.2	40.0	40.2
Sexual intercourse in last 3 months					
Yes	33.3	35.2	33.7	33.0	32.7
No	66.7	64.8	66.3	67.0	67.4

Percentages are adjusted for survey weights, the question taught about AIDs in school is not available for states that participated in the 2015 sample (n=461,218 for 2001-2015), n= number, HPV = human papillomavirus, AIDS = acquired immune deficiency syndrome, condom use is restricted to students who reported having sexual intercourse in the last 3 months

similar to students in states without HPV legislation in terms of gender, grade, race, smoking, and alcohol use before and after most states passed legislation in 2007 (Table 2.1). The average age of students in states with legislation was 16.0 years old and in states without legislation was 16.1 years old. States with legislation and states without legislation had a similar percent of students who ever had been taught about AIDS in school, with a higher percent being taught about AIDS in school prior to 2007 (91.8%) than after 2007 (89.2%). The percentage of students ever having sexual intercourse in the last 3 months and the percentage of students reporting condom use during last sexual intercourse was similar for states with and without HPV legislation and decreased slightly from prior to 2007 to after 2007.

Difference-in-difference models showed no substantive or statistically significant changes in recent sexual intercourse or condom use (Table 2.2). Figure 2.1 plots trends in adolescent sexual behaviors from 2001 to 2015, where most legislation was enacted in 2007, and it shows no difference in risky sexual behaviors in states with legislation compared to states without legislation. The difference-in-difference estimates were consistent with this. Students in states passing HPV legislation decreased recent sexual intercourse by 0.90 percentage points (95% CI (-2.33, 0.52), p value = 0.21) and increased condom use during last sexual encounter by 0.96 percentage points (95% CI (-0.97, 2.89), p value = 0.32) compared to students in states without legislation. When the results were separated by the type of legislation there continued to be no significant difference sexual intercourse or condom use for states with HPV legislation compared to states without HPV legislation; however, HPV legislation regarding cost and access seemed to have a larger impact on teen sexual behaviors than HPV legislation regarding education. For legislation regarding education, recent sexual intercourse decreased by 0.072 percentage points (95% CI (-1.93, 1.79), p value = 0.94) and condom use decreased by 0.22

Table 2.2: Change in the proportion of sexual behaviors in states with legislation compared to states without legislation

	Sexual Intercourse during the last 3 months			Condom use during last sexual intercourse		
	Percentage Point Change	(95% CI)	p value	Percentage Point Change	(95% CI)	p value
Among All Students						
Any Legislation	-0.90	(-2.33, 0.52)	0.21	0.96	(-0.97, 2.89)	0.32
Legislation about vaccine cost and accessibility	-1.30	(-2.78, 0.17)	0.08	1.48	(-0.99, 3.95)	0.23
Legislation about HPV education	-0.072	(-1.93, 1.79)	0.94	-0.22	(-2.50, 2.06)	0.85
Among Different Student Populations (Any Legislation)						
Gender						
Males	-0.67	(-2.47, 1.14)	0.46	0.047	(-2.41, 2.51)	0.97
Females	-1.11	(-2.59, 0.37)	0.14	1.78	(-0.82, 4.37)	0.18
Age						
<17	-1.07	(-2.49, 0.34)	0.13	1.64	(-0.94, 4.23)	0.21
17 or 18	-0.52	(-2.67, 1.64)	0.63	0.44	(-1.97, 2.86)	0.71
Race/Ethnicity						
White	-0.96	(-2.65, 0.73)	0.26	0.83	(-1.59, 3.25)	0.49
Black/Hispanic/Other	-0.55	(-2.28, 1.18)	0.52	2.06	(-0.76, 4.87)	0.15

Each cell represents a separate regression with the dependent variables noted in the columns. For each dependent variable, the model includes survey year fixed effects, age, gender, and current grade fixed effects. Models include state-specific linear time trends and state fixed effects, CI = confidence interval, HPV = human papillomavirus

percentage points (95% CI (-2.50, 2.06), p value= 0.85). For legislation regarding vaccination cost, recent sexual intercourse decreased by 1.30 percentage points (95% CI (-2.78, 0.17), p value=0.08) and condom use increased by 1.48 percentage points (95% CI (-0.99, 3.95), p value= 0.23).

In additional analyses, we did not find evidence that the parallel trends assumption was violated (Supplemental Table 2.2). Sub-group analyses showed some difference by age, gender and ethnicity, but no group showed statistically significant increases in any sexual behaviors

Figure 2.1: Adolescent sexual behaviors over time in states with HPV legislation and states without HPV legislation

Figure 2.1a: Sexual intercourse during the last 3 months

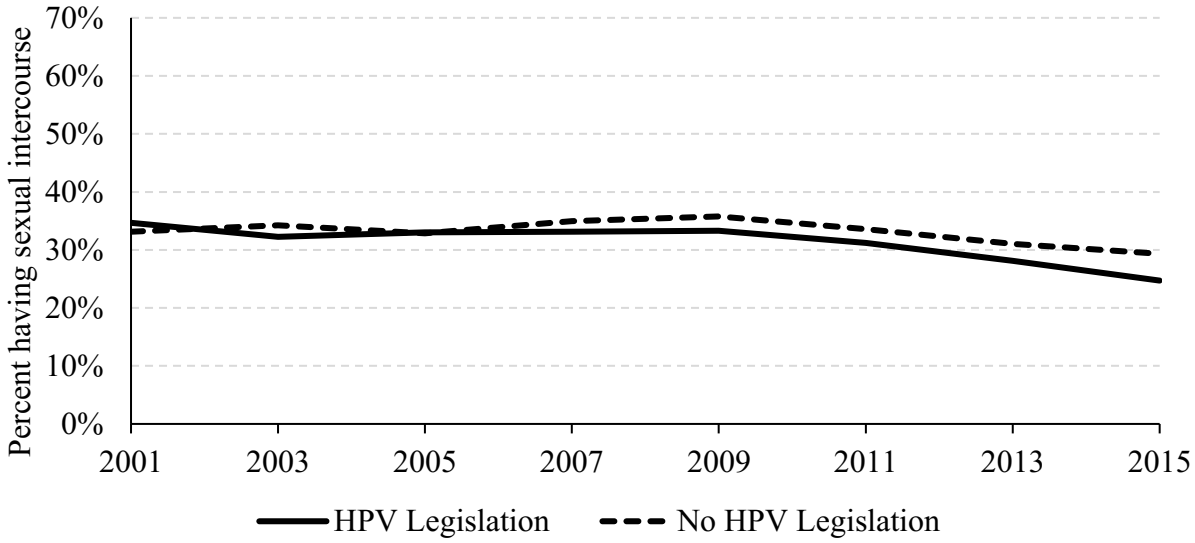


Figure 2.1b: Condom use during last sexual intercourse

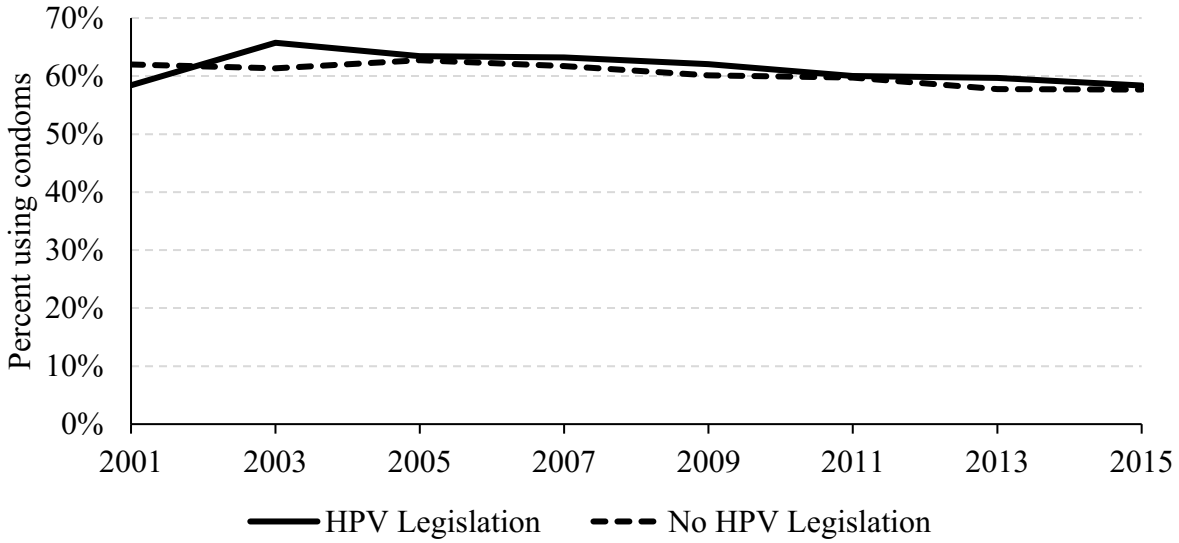


Figure 1a shows the percent of adolescents every having sexual intercourse over the last 3 months for states that passed HPV legislation (solid black line) and states that did not pass HPV legislation (dashed black line). Figure 1b shows the percent of adolescents using condoms the last time they had sexual intercourse for states that passed HPV legislation (solid black line) and states that did not pass HPV legislation (dashed black line). Most states that passed HPV legislltion did so in 2007. The first HPV vaccination was FDA approved in 2006.

Table 2.3: Change in the average number of sexual partners in the last 3 months in states with legislation compared to states without legislation

	Number of sexual partners in last 3 months		
	Average Number Change	(95% CI)	p value
Among All Students			
Any Legislation	-0.020	(-0.050, 0.010)	0.18
Legislation about vaccine cost and accessibility	-0.041	(-0.072, -0.0097)	0.01
Legislation about HPV education	0.011	(-0.017, 0.039)	0.44
Among Different Student Populations (Any Legislation)			
Gender			
Males	-0.032	(-0.080, 0.016)	0.18
Females	-0.0096	(-0.030, 0.011)	0.35
Age			
<17	-0.022	(-0.052, 0.0082)	0.15
17 or 18	-0.013	(-0.056, 0.030)	0.55
Race/Ethnicity			
White	-0.013	(-0.047, 0.022)	0.47
Black/Hispanic/Other	-0.025	(-0.065, 0.016)	0.22

Each row represents a separate regression. The models include survey year, state, age, gender, and current grade fixed effects, and state-specific linear time trends. CI=confidence interval, HPV=human papillomavirus

after the policy. It appeared that females had larger decreases in recent sexual intercourse and had larger increases in condom use than males. Students under age 17 had larger decreases in recent sexual intercourse and larger increases in condom use than students age 17 or 18. There were no differences seen by race/ethnicity for number of sexual partners. Whites saw a smaller percentage point increase in condom use than blacks, Hispanics, and other race/ethnicities. There was no difference when CHIP, Medicaid, political party, unemployment, teen pregnancy rates, and sexually transmitted disease rates were included in the models (Supplemental Table 2.3). Analyses examining lagged impacts suggested a substantive, but not statistically significant 6.1 percentage point decrease (p=0.009) in recent sexual intercourse and a 5.9 percentage point increase (p=0.046) in condom use (pre-specified p-value threshold p<0.003) (Supplemental table 2.4). Results did not differ for the secondary outcome examined of number of sexual partners

during the last three months. For the secondary outcome of number of sexual partners in the last three months, there was a non-significant decrease in the number of sexual partners by 0.02 (p=0.18) in states that enacted HPV legislation compared to states that did not enact HPV legislation (Table 2.3). Lastly, as expected, the estimates from models including the YRBSS sample weights were less precisely estimated, but the interpretation of the main effects was similar (Supplemental Table 2.5).

DISCUSSION

In this national study, we found no association between the passage of legislation designed to increase uptake of the HPV vaccine and sexual behaviors among high school-going adolescents in the United States. This finding was consistent across subgroups and robust to different specifications and sensitivity tests.

Despite long-standing knowledge of the protective benefits of the HPV vaccine, vaccination rates in the United States remain low.[28] Even among those receiving the vaccine, the timing of HPV vaccination often occurs after sexual debut and HPV exposure, reducing its potential efficacy. A study conducted in the National Health and Nutrition Examination Survey (NHANES) found that 43% of girls with at least one dose of the HPV vaccine had sex before or during the same year as their first HPV vaccination.[29] Ensuring that adolescents receive the HPV vaccination before their first sexual experience is important to helping prevent the negative health effects of HPV infections. Policies to educate adolescents and their families about the benefits of vaccination and increase access will likely be an important part of the policy response to improve vaccination rates.

Thus far, the literature has found minimal, if any, benefits of these policies on vaccination rates.[30-33] In states that have implemented these policies, the ultimate legislation

passed was often less expansive than other debated options. The less expansive options passed included additions such as opt-out options for vaccine mandates that may have reduced the number of adolescents vaccinated, and weakening of the policy to just be educational.[30] The weakening of the legislation was in part due to concerns about behavioral responses to the policy, in addition to a number of other concerns around ethics, health benefits, and side effects.[14-16] Our study shows that the policy options implemented thus far have not raised the risk of risky sexual activity. Additionally, adolescents appear to be engaged in less sexual intercourse over time, even with increasing availability of HPV vaccination. The percentage of adolescents that have ever had sex, that had sex before age 13, and that had sex with four or more people has decreased from 1991 to 2015 and adolescent pregnancy rates have dropped from 1990 to 2014.[34,35] However, we found that condom use during last sexual intercourse appeared to decrease slightly from 2001 to 2015. Our findings and this broader context both support calls to adopt stronger vaccination education and access policies.

This study is subject to a number of limitations. First, we considered the effects of passage of HPV-related legislation, which may differ from the actual consequences of policy implementation. Second, similar policies in different states may have been implemented very differently. Data on exact implementation were not available and therefore we were not able to assess heterogeneity in policy effects across states. Third, we only examined legislative rulings regarding HPV vaccination. Many states may be providing HPV education and funding through state Public Health Departments that do not require legislation. Non-legislative HPV initiatives were not accounted for in our analysis due to the difficulty in finding this data. Fourth, any unobserved or omitted state-year confounders that are correlated with both the HPV legislation and the adolescent sexual behavior outcomes could bias our analysis. We attempted to adjust for

these potential confounders in a variety of ways and conducted several sensitivity checks. However, we cannot fully rule out the possibility of residual bias.

Fifth, there is missing data on the number of sexual partners (19.4%) and condom use (3.2%) which may create a selection bias if students not reporting their sexual behaviors did so in a way that was also related to their state's HPV legislation policy. For example, if students with riskier behaviors are less likely to report their behaviors on the survey, and they are more likely to live in states that passed HPV legislation, we may be worried about selection bias. However, it seems that teens reporting of their sexual behaviors may not be related to their state's HPV legislation policy, so we are not strongly concerned about this bias. Sixth, we also do not have complete information on all states with HPV legislation policies in the YRBSS state survey sample, so our results, while coming from a wide regional distribution in the US, should take into account that results may not be generalizable to states not included in the analysis.

Conclusion

HPV legislation does not appear to have a detrimental effect on adolescent sexual behaviors. This study, taken with the other studies looking at the impact of HPV vaccines on adolescent sexual behavior and the low vaccination rates in the United States, provide support for the reintroduction and strengthening of legislation regarding the HPV vaccine. Concern that legislation will increase risky adolescent sexual behaviors should not be used when deciding to pass legislation regarding HPV vaccination.

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Appendix Table 2.1: Type and year of HPV legislation passed by states

State	Type of Legislative Action: Vaccine Cost and Accessibility[a]	HPV Education[b]	Mandate	Legislation
Included in State YRBSS Analysis				
Iowa	2008	2007		H.F. 611 (2007), H.F. 2145 (2008)
Louisiana		2008		H.B. 359 – Act 210
Maine	2007			Maine Chapter No. 73 (L.D. 137)
Maryland		2007		Md. Chapter No. 191 (H.B. 1049), Chapter No. 190 (S.B. 774)
Michigan		2008		H.B. 5322 (S.B. 415) – Public Act 121
Missouri		2009		S.B. 104, H.B. 1375
Nevada	2007			Nev. Chapter No. 257 (S.B. 409)
New Jersey		2007		NJ Chapter No. 134 (S. 2286)
New Mexico	2007	2007		H.J.M. 39, NM Chapter No. 278 (S.B. 207)
New York	2007			NY Chapter No. 54 (A.B. 4304)
North Carolina		2007		NC Session Law 2007-59 (S.B. 260)
North Dakota		2007		ND Chapter No. 232 (H.B. 1471)
Rhode Island	2007		2015	H.B. 5061 (2007), Department of Health (2015)
South Dakota	2007			H.B. 1061
Texas		2007		H.B. 1379
Utah		2007		H.B. 358
Not included in State YRBSS Analysis				
Colorado	2007	2007		Co. Chapter No. 41 (S.B. 97), Co. Chapter No. 212 (H.B. 1292), Co. Chapter No. 318 (H.B. 1301)
District of Columbia			2007	B-17-0030
Illinois[c]	2007	2007		Public act 095-0422 (S.B. 937)
Indiana	2013	2007		Public Law No. 80 (S.B. 0327) (2007), Public Law No. 113 (H.B. 1464) (2013)
Minnesota		2007		MN Laws, Chapter 147 (H.F. 1078)
Oregon	2009	2013		Chapter No. 630 (H.B. 2794) (2009), Chapter No. 348 (S.B. 722) (2013)
Virginia[c]			2007	Va. Chapter No. 922 (S.B. 1230), Va. Chapter No. 858 (H.B. 2035)
Washington		2007		Wash. Chapter No. 276 (H.B. 1802)

[a] Vaccine cost and accessibility includes legislation regarding insurance coverage of vaccines, funding for vaccines, and need of a prescription to get the vaccine, [b] HPV education includes legislation regarding student and/or parent education, general HPV awareness, funds for research and task force creation; [c] Illinois and Virginia were included in YRBSS but didn't have data before and after the legislation passed in YRBSS

Control states: Alabama, Alaska, Arizona, Arkansas, California, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Kansas, Kentucky, Mississippi, Montana, Nebraska, New Hampshire, Oklahoma, Pennsylvania, South Carolina, Tennessee, Vermont, West Virginia, Wisconsin, Wyoming

Appendix Table 2.2: Pre-trend analysis of the change in the proportion of sexual behaviors in states with any HPV legislation compared to states without legislation

Outcome	Coefficient for year x legislation interaction (95% CI)	p value
Number of sexual partners in last three months	-0.0023 (-0.014, 0.0090)	0.68
Condom use during last sexual intercourse	-0.00080 (-0.0065, 0.0049)	0.78
Ever had sex in the last three months	0.000057 (-0.0047, 0.0048)	0.98

CI = confidence interval, HPV= human papillomavirus

Appendix Table 2.3: Change in the proportion of sexual behaviors in states with legislation compared to states without legislation after adjusting for CHIP, Medicaid, teen pregnancy rates, sexually transmitted disease rates, unemployment rates, and political party of the state legislature and governor

	Sexual intercourse during the last 3 months			Condom use during last sexual intercourse		
	Percentage Point Change	(95% CI)	p value	Percentage Point Change	(95% CI)	p value
Among All Students						
Any Legislation	-1.14	(-2.71, 0.43)	0.15	0.86	(-1.12, 2.85)	0.38
Legislation about vaccine cost and accessibility	-1.96	(-3.52, -0.40)	0.015	1.36	(-1.61, 4.33)	0.36
Legislation about HPV education	0.099	(-1.67, 1.87)	0.91	-0.17	(-2.42, 2.08)	0.88
Among Different Student Populations (Any Legislation)						
Gender						
Males	-0.99	(-2.79, 0.81)	0.27	0.24	(-2.39, 2.86)	0.86
Females	-1.28	(-3.16, 0.61)	0.18	1.44	(-1.18, 4.06)	0.27
Age						
<17	-1.13	(-2.55, 0.29)	0.12	1.64	(-0.97, 4.25)	0.21
17 or 18	-0.99	(-3.35, 1.38)	0.40	0.11	(-2.72, 2.94)	0.94
Race/Ethnicity						
White	-1.40	(-3.23, 0.43)	0.12	0.37	(-1.76, 2.50)	0.73
Black/Hispanic/Other	-0.45	(-2.43, 1.52)	0.64	2.61	(-0.66, 5.88)	0.12

Each cell represents a separate regression with the dependent variables noted in the columns. For each dependent variable, the model includes survey year fixed effects, age, gender, and current grade fixed effects. Models include state-specific linear time trends, state fixed effects and include CHIP, Medicaid, unemployment rates, teen pregnancy rates, sexually transmitted disease rates among teens 15-19, majority political party for the state legislature, and political party of the governor, CI = confidence interval, HPV = human papillomavirus, CHIP = Children's Health Insurance Program

Appendix Table 2.4: Lead and lag analysis of the change in the proportion of sexual behaviors in states with any HPV legislation compared to states without legislation

	Sexual intercourse during the last 3 months			**Condom use during last sexual intercourse**		
	Percentage Point Change	(95% CI)	p value	Percentage Point Change	(95% CI)	p value
7+ Year Lead	3.95	(-1.49, 9.39)	0.15	-3.92	(-12.0, 4.16)	0.33
5-6 Year Lead	2.65	(-0.31, 5.60)	0.08	-3.35	(-7.92, 1.21)	0.15
3-4 Year Lead	0.55	(-1.61, 2.71)	0.61	-0.053	(-2.78, 2.67)	0.97
1-2 Year Lead	-	-	-	-	-	-
0-1 Year Lag	-2.73	(-5.10, -0.36)	0.025	2.42	(-0.48, 5.31)	0.10
2-3 Year Lag	-4.46	(-7.55, -1.38)	0.006	5.46	(1.02, 9.91)	0.017
4-5 Year Lag	-6.08	(-10.5, -1.64)	0.009	5.94	(0.11, 11.8)	0.046
6+ Year Lag	-8.75	(-15.0, -2.47)	0.008	8.64	(0.050, 17.2)	0.049

Each column represents a separate regression with the dependent variables noted in the columns. For each dependent variable, the model includes survey year fixed effects, age, gender, and current grade fixed effects. Models include state-specific linear time trends and state fixed effects. The reference category for this regression was a 1-2 year lead, CI = confidence interval, HPV = human papillomavirus

Appendix Table 2.5: Change in proportion of adolescent sexual behaviors in states with legislation compared to states without legislation including YRBSS sample weights in the regression

	Sexual Intercourse during the last 3 months			Condom use during last sexual intercourse		
	Percentage Point Change	(95% CI)	p value	Percentage Point Change	95% CI	p value
Among All Students						
Any Legislation	0.0019	(-1.71, 1.71)	0.99	-0.99	(-3.19, 1.22)	0.37
Legislation about vaccine cost and accessibility	-0.14	(-1.25, 0.97)	0.80	1.57	(-1.07, 4.21)	0.24
Legislation about HPV education	0.12	(-2.07, 2.32)	0.91	-2.05	(-3.86, -0.25)	0.03
Among Different Student Populations (Any Legislation)						
Gender						
Males	-0.27	(-2.10, 1.55)	0.77	-2.60	(-6.61, 1.41)	0.20
Females	0.20	(-1.98, 2.37)	0.86	0.53	(-1.30, 2.36)	0.56
Age						
<17	-1.19	(-2.44, 0.055)	0.06	0.46	(-1.23, 2.14)	0.59
17 or 18	2.12	(-0.81, 5.06)	0.15	-2.29	(-5.96, 1.39)	0.22
Race/Ethnicity						
White	-0.67	(-2.03, 0.69)	0.33	-0.89	(-5.43, 3.66)	0.70
Black/Hispanic/Other	1.41	(-1.47, 4.28)	0.33	-1.14	(-4.28, 1.99)	0.47

Each cell represents a separate regression with the dependent variables noted in the columns. For each dependent variable, the model includes survey year fixed effects, age, gender, and current grade fixed effects. Models include state-specific linear time trends, state fixed effects, and survey weights, CI = confidence interval, HPV = human papillomavirus, YRBSS = Youth Risk Behavioral Surveillance System

Prospective Evaluation of the Impact of Stress, Anxiety, and Depression on Household Income among Young Women with Early Breast Cancer

Erin E. Cook, MPH; Shoshana M Rosenberg, ScD, MPH; Kathryn J Ruddy, MD, MPH; William T. Barry, PhD; Mary Greaney, PhD; Jennifer Ligibel, MD; Kim Sprunck-Harrild, MSW, MPH; Michelle D. Holmes, MPH, MD, DrPH; Rulla M. Tamimi, ScD; Jane J. Kim, PhD; Karen M. Emmons, PhD; Ann H. Partridge, MD, MPH.

ABSTRACT

Objective: To determine if baseline stress, anxiety, and depression are associated with changes in household income in young women with breast cancer.

Methods: The Young and Strong trial enrolled 467 women ages 18-45, newly diagnosed with early breast cancer from 2012-2013, 76% (N=356) of whom responded to income survey questions. Change in household income from baseline to 12 months was assessed and women were categorized as having lost, gained, maintained the same income <$100,000, and maintained income ≥ $100,000. Patient reported stress, anxiety, and depression were assessed at baseline. Adjusted multinomial logistic regression models were used to compare women who lost, gained, or maintained income ≥ $100,000 to women maintaining the same income <$100,000.

Results: Although most women maintained incomes ≥ $100,000 (37.1%) or the same income <$100,000 (32.3%), 15.4% of women lost income and 15.2% of women gained income. Women maintaining incomes ≥ $100,000 were more likely to be more educated, married, and have stage I disease. Stress, anxiety, and depression were not associated with gaining or losing income compared to women maintaining the same incomes <$100,000. Women with incomes <$50,000 had a higher risk of losing income compared to women with incomes ≥ $50,000 (RR=2.23, 95% CI (1.04, 4.78)).

Conclusions: Baseline stress, anxiety, and depression were not associated with income changes for young women with breast cancer. However, lower baseline income was associated with losing household income; further support for these women should be considered.

INTRODUCTION

While 4% of breast cancer cases were diagnosed among women under age 40, breast cancer was the most common cancer among women ages 15-39 in the US.[1,2] The disease is aggressive in young women, but the 5-year survival for women ages 35-39 is still nearly 90%.[2,3] Nevertheless, young women report lower quality of life (QOL) and higher levels of stress than older women with breast cancer.[4-7] This may be in part due to the burden of employment and financial disturbances after treatment in younger cancer survivors.[4,5,7-9] These financial and employment disturbances can impact both the woman with cancer and her family members.[10] This study aimed to determine if stress, anxiety, or depression is associated with household income changes for young women with breast cancer.

METHODS

Study Population

The randomized trial, Young and Strong: An Education and Supportive Care Intervention Study for Young Women with Breast Cancer (Trial Registration: NCT01647607), provided data for this study.[11,12] This trial enrolled 467 English-speaking women ages 18-45 with newly diagnosed stage I-III breast cancer. Enrollment occurred from 7/2012-12/2013 at 14 academic and 40 community practices around the US. Practices were randomized to the Young Women's Intervention (YWI) or the Physical Activity Intervention (PAI). The YWI contained information about fertility, genetic testing, physical activity, and survivorship. The PAI contained information about physical activity. Participants completed surveys at baseline, 3, 6, and 12 months. Baseline assessment often occurred at the first medical oncology visit.

Since the YWI discussed how breast cancer impacts employment, we examined if intervention arm impacted change in income and found no statistically significant associations

(Appendix 3.1). Thus, we combined the YWI and PAI arms for the rest of this analysis. Women who did not respond to the 12-month survey (N=51), had stage IV disease (N=2), and did not report household income on the baseline and 12-month surveys (N=58) were excluded, leaving an analytic sample of 356 women. Women excluded for missing income information tended to be older and less educated than women included (Appendix 3.2).

Exposures

The main exposures were baseline measures of stress, anxiety, and depression. Stress was measured using the Perceived Stress Scale (PSS) with categories of low (<14), moderate (14-26), or high (≥ 27) stress.[13] Anxiety was measured from the Hospital Anxiety and Depression Scale (HADS) anxiety subscale with categories of normal (<8), borderline anxious (8-10), or anxious (≥ 11).[14,15] Depression was measured by the Center for Epidemiological Studies Depression Scale (CES-D) and was a binary variable of no depression (<16) or depression (≥ 16).[16] We used the CES-D over the HADS depression subscale due to its better ability to detect major depression.[17]

Outcomes

The primary outcome was change in household income between the baseline and 12-month survey. Women reported their household income from all sources before taxes in a categorical variable (<$5,000, $5,000-$11,999, $12,000-$15,999, $16,000-$24,999, $25,000-$34,999, $35,000-$49,999, $50,000-$74,999, $75,000-$99,999, and ≥ $100,000). We created a categorical variable for change in household income: losing, gaining, maintaining ≥$100,000, or maintaining same income <$100,000. We were unable to determine how incomes changed if women maintained ≥ $100,000 based on the categories of the income question (ex: $150,000 to $200,000 or vice versa). Therefore, we separated women who reported the same income category

at baseline and 12-months into <$100,000 and ≥ $100,000. Women were categorized as losing or gaining income, regardless of their income category, if they reported a different income category at baseline and 12-months.

Women reported financial, insurance, and working concerns on the 3- and 12-month surveys. For all women we examined employment status and responses to the questions "I have financial problems" and "I have insurance problems." Employed women were asked: "I have difficulty talking to people who work with me about the cancer," "I have difficulty asking for time off work for medical treatments," and "I am worried about being fired." Unemployed women were asked if they looked for work in the past month. Responses to these questions were categorized as no if respondents reported "not at all" or "a little" and yes if respondents reported "a fair amount," "much," or "very much."

Statistical Analysis

Descriptive statistics, including the number, percentage, and chi-square or Fisher's exact test (≤ 5 women), were calculated by change in income for demographic, cancer, psychosocial, employment, and financial information. Separate multinomial logistic regression models, with the reference category being same income <$100,000, analyzed how stress, anxiety, and depression were associated with changes in income. Models were adjusted for age (continuous), race/ethnicity (Hispanic, black, other vs. white), marital status (yes vs. no), children (yes vs. no), stage, and baseline income (≥ $50,000 vs. <$50,000). We performed multiple sensitivity analyses. First, we did not have employment information at baseline, so we added 3-month employment status as a proxy. Second, we created propensity scores and included them as quintiles in the regression models. Lastly, since the survey income categories were not uniform ranges ($5,000-$25,000), we grouped women into even income categories at baseline and 12

months (<$25,000, $25,000-$49,999, $50,000-$74,999, $75,000-$99,999, and ≥ $100,000). From these categories we looked at women who lost, gained, same <$100,000, and maintained ≥ $100,000.

Results were considered statistically significant if $p<0.05$. SAS 9.4 was used for the cluster randomized analyses and StataIC 14 was used for the remaining analyses.[18,19] The study was approved by the Dana-Farber Cancer Institute Institutional Review Board, which oversaw most of the study sites via; however, some sites maintained their own institutional review. Written informed consent was obtained from all participants prior to study enrollment.

RESULTS

Over 12 months, 37% of women maintained incomes ≥ $100,000, 32% maintained the same income <$100,000, 15% gained income, and 15% lost income (Table 3.1). Women in the income change categories were similar in terms of demographic, cancer, and psychosocial measures. However, women maintaining ≥ $100,000 were more likely to be more educated, married, and have stage I disease. They were less likely to have chemotherapy and depression. High stress ranged from 3.1% of women maintaining ≥ $100,000 to 13.2% of women losing income. Anxiety ranged from 30.7% of women with the same income <$100,000 to 42.4% of women gaining income. Depression ranged from 31.5% of women maintaining ≥ $100,000 to 54.0% of women losing income. Among women who lost or gained income, the estimated dollar amount of change in income was similar (Appendix 3.3).

Psychosocial measures were not associated with losing, gaining, or maintaining incomes ≥ $100,000 compared to maintaining the same income <$100,000 (Table 3.2). There was no association between high stress (RR=2.42, 95% CI (0.72, 8.08)), anxiety (RR=1.12, 95% CI (0.50, 2.50)), or depression (RR=1.41, 95% CI (0.70, 2.85)) and losing income. Baseline income

Table 3.1: Participant characteristics at baseline survey by change in household income

	Change in Household Income				
	Maintain ≥ $100,000 (N=132) N. (%)	**Same <$100,000 (N=115)** N. (%)	**Gained (N=54)** N. (%)	**Lost (N=55)** N. (%)	p value
Demographics					
Age					0.16
<35	18 (13.6)	30 (26.1)	13 (24.1)	15 (27.3)	
35-39	38 (28.8)	23 (20.0)	15 (27.8)	11 (20.0)	
40-45	76 (57.6)	62 (53.9)	26 (48.2)	29 (52.7)	
Education					<0.0001[a]
≤High School	1 (0.8)	13 (11.3)	11 (20.4)	10 (18.2)	
≥Some College	131 (99.2)	102 (88.7)	43 (79.6)	45 (81.8)	
Married					<0.0001
Yes	122 (92.4)	82 (71.3)	43 (79.6)	41 (74.6)	
No	10 (7.6)	33 (28.7)	11 (20.4)	14 (25.5)	
Children					0.07
Yes	107 (81.1)	78 (67.8)	36 (67.7)	40 (74.1)	
No	25 (18.9)	37 (32.2)	18 (33.3)	14 (25.9)	
Race/Ethnicity					0.31
Non-Hispanic, White	108 (81.8)	85 (74.6)	38 (70.4)	41 (74.6)	
Hispanic, black, other	24 (18.2)	29 (25.4)	16 (29.6)	14 (25.5)	
Region					0.19
Northeast	38 (28.8)	30 (26.1)	11 (20.4)	12 (21.8)	
South/Southeast	22 (16.7)	34 (29.6)	18 (33.3)	18 (32.7)	
Midwest	46 (34.9)	38 (33.0)	15 (27.8)	18 (32.7)	
West	26 (19.7)	13 (11.3)	10 (18.5)	7 (12.7)	
Change in Employment					0.23[a]
None-Employed	85 (68.0)	66 (62.3)	26 (54.2)	33 (63.5)	
None-Unemployed	20 (16.0)	20 (18.9)	11 (22.9)	15 (28.9)	
Lost	1 (0.8)	0 (0.0)	1 (2.1)	0 (0.0)	
Gained	19 (15.2)	20 (18.9)	10 (20.8)	4 (7.7)	
Household Income					<0.0001
<$50,000	0 (0.0)	32 (27.8)	37 (68.5)	23 (41.8)	
$50,000-$99,999	0 (0.0)	83 (72.2)	17 (31.5)	21 (38.2)	
≥ $100,000	132 (100.0)	0 (0.0)	0 (0.0)	11 (20.0)	
Cancer					
Stage					0.01
I	62 (47.0)	39 (33.9)	12 (22.2)	14 (25.5)	
II	54 (40.9)	61 (53.0)	31 (57.4)	28 (50.9)	
III	16 (12.1)	15 (13.0)	11 (20.4)	13 (23.6)	
Estrogen Receptor					0.19
Positive	107 (81.1)	82 (71.3)	37 (68.5)	40 (72.7)	
Negative	25 (18.9)	33 (28.7)	17 (31.5)	15 (27.3)	
Progesterone Receptor					0.39
Positive	99 (75.0)	79 (68.7)	36 (66.7)	35 (63.6)	
Negative	33 (25.0)	36 (31.3)	18 (33.3)	20 (36.4)	
HER2					0.91
Positive	30 (23.1)	26 (22.8)	12 (22.2)	15 (27.3)	
Negative	100 (76.9)	88 (77.2)	42 (77.8)	40 (72.7)	

Table 3.1 Continued: Participant characteristics at baseline survey by change in household income

	Change in Household Income				
	Maintain ≥ $100,000 (N=132) N. (%)	**Same <$100,000 (N=115)** N. (%)	**Gained (N=54)** N. (%)	**Lost (N=55)** N. (%)	p value
Baseline Cancer Treatment					
Chemotherapy					0.01
Yes/Planned	96 (73.3)	97 (85.8)	48 (88.9)	48 (88.9)	
No	35 (26.7)	16 (14.2)	6 (11.1)	6 (11.1)	
Radiation					0.05
Yes/Planned	69 (61.6)	59 (64.8)	39 (83.0)	31 (72.1)	
No	43 (38.4)	32 (35.2)	8 (17.0)	12 (27.9)	
Endocrine Therapy					0.53
Yes/Planned	97 (78.9)	78 (72.2)	34 (69.4)	37 (74.0)	
No	26 (21.1)	30 (27.8)	15 (30.6)	13 (26.0)	
Baseline Psychosocial Measures					
Stress					0.15[a]
Low	52 (40.3)	42 (37.8)	16 (30.2)	14 (26.4)	
Moderate	73 (56.6)	61 (55.0)	32 (60.4)	32 (60.4)	
High	4 (3.1)	8 (7.2)	5 (9.4)	7 (13.2)	
Anxiety					0.73
Normal	55 (42.0)	50 (43.9)	19 (35.9)	20 (37.7)	
Borderline	31 (23.7)	29 (25.4)	11 (20.8)	16 (30.2)	
Anxiety	45 (34.4)	35 (30.7)	23 (42.4)	17 (32.1)	
Depression					0.03
No	85 (68.6)	63 (58.3)	27 (54.0)	23 (46.0)	
Yes	39 (31.5)	45 (41.7)	23 (46.6)	27 (54.0)	

([a])Fisher's exact test; N=Number; missing: 1 children, 1 race/ethnicity, 25 employment, 3 HER2, 4 chemotherapy, 63 radiation, 26 endocrine therapy, 10 stress, 5 anxiety, 24 depression; 100% had/planned surgery

Table 3.2: Adjusted multinomial logistic regression analysis of stress, anxiety and depression's impact on change in household income

	Lost vs. Same <$100,000		Gained vs. Same <$100,000		Maintain ≥ $100,000 vs. Same <$100,000	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
Stress						
Low	Ref.		Ref.		Ref.	
Moderate	1.35 (0.63, 2.91)	0.44	0.96 (0.43, 2.14)	0.91	0.97 (0.55, 1.74)	0.93
High	2.42 (0.72, 8.08)	0.15	1.47 (0.38, 5.72)	0.58	0.43 (0.11, 1.65)	0.22
Anxiety						
Normal	Ref.		Ref.		Ref.	
Borderline	1.16 (0.50, 2.67)	0.73	0.88 (0.34, 2.28)	0.80	1.05 (0.52, 2.11)	0.89
Anxiety	1.12 (0.50, 2.50)	0.79	1.50 (0.65, 3.47)	0.34	1.26 (0.66, 2.40)	0.48
Depression						
No	Ref.		Ref.		Ref.	
Yes	1.41 (0.70, 2.85)	0.34	0.90 (0.42, 1.93)	0.78	0.73 (0.41, 1.31)	0.29
Covariates Only						
Age	0.99 (0.93, 1.05)	0.71	1.01 (0.94, 1.08)	0.86	1.04 (0.98, 1.10)	0.15
Cancer Stage						
I	Ref.		Ref.		Ref.	
II	1.36 (0.62, 2.98)	0.57	1.64 (0.70, 3.84)	0.26	0.64 (0.35, 1.14)	0.13
III	2.68 (0.98, 7.37)	0.06	2.72 (0.88, 8.37)	0.08	0.75 (0.31, 1.83)	0.53
Married						
No	Ref.		Ref.		Ref.	
Yes	1.69 (0.72, 3.92)	0.23	3.76 (1.50, 9.41)	0.005	2.56 (1.08. 6.06)	0.03
Children						
No	Ref.		Ref.		Ref.	
Yes	1.21 (0.53, 2.76)	0.65	0.71 (0.30, 1.65)	0.42	1.49 (0.76, 2.92)	0.25
Race/Ethnicity						
Non-Hispanic, White	Ref.		Ref.		Ref.	
Hispanic, black, other	1.26 (0.57, 2.76)	0.57	1.32 (0.59, 3.06)	0.49	1.10 (0.56, 2.19)	0.78
Baseline Income						
≥ $50,000	Ref.		Ref.			
< $50,000	2.23 (1.04, 4.78)	0.04	8.47 (3.87, 18.81)	<0.0001		

Separate models were run for stress, anxiety, depression and covariates only; models were adjusted for age, marriage, children, stage, race/ethnicity, and baseline income; CI=confidence interval; RR=risk ratio

Table 3.3: Measures of work, financial, and insurance worries by change in household income

	3 Months					12 Months				
	Maintain ≥ $100,000	**Same <$100,000**	**Gained**	**Lost**		**Maintain ≥ $100,000**	**Same <$100,000**	**Gained**	**Lost**	
	N. (%)	N. (%)	N. (%)	N. (%)	p value	N. (%)	N. (%)	N. (%)	N. (%)	p value
All Women										
Financial Problems					<0.0001					<0.0001
No	119 (90.2)	77 (67.0)	31 (57.4)	25 (45.5)		120 (90.9)	75 (65.2)	34 (63.0)	23 (41.8)	
Yes	7 (5.3)	31 (27.0)	17 (31.5)	27 (49.1)		10 (7.6)	39 (33.9)	20 (37.0)	31 (56.4)	
Missing	6 (4.6)	7 (6.1)	6 (11.1)	3 (5.5)		2 (1.5)	1 (0.9)	0 (0.0)	1 (1.8)	
Insurance Problems					<0.0001					0.02
No	122 (92.4)	99 (86.1)	36 (66.7)	37 (67.3)		124 (93.9)	106 (92.2)	48 (88.9)	42 (76.4)	
Yes	4 (3.0)	9 (7.8)	12 (22.2)	14 (25.5)		7 (5.3)	8 (7.0)	6 (11.1)	11 (20.0)	
Missing	6 (4.6)	7 (6.1)	6 (11.1)	4 (7.3)		1 (0.8)	1 (0.9)	0 (0.0)	2 (3.6)	
Currently Working					0.50					0.37
No	40 (30.3)	41 (35.7)	21 (38.9)	19 (34.6)		22 (16.7)	22 (19.1)	13 (24.1)	16 (29.1)	
Yes	86 (65.2)	66 (57.4)	27 (50.0)	33 (60.0)		109 (82.6)	92 (80.0)	41 (75.9)	38 (69.1)	
Missing	6 (4.6)	8 (7.0)	6 (11.1)	3 (5.5)		1 (0.8)	1 (0.9)	0 (0.0)	1 (1.8)	
Employed Women										
Difficulty talking to coworkers					0.61					0.76
No	78 (90.7)	58 (87.9)	22 (81.5)	29 (87.9)		97 (89.0)	84 (91.3)	35 (85.4)	34 (89.5)	
Yes	8 (9.3)	8 (12.1)	5 (18.5)	4 (12.1)		12 (11.0)	8 (8.7)	6 (14.6)	4 (10.5)	
Difficulty asking for time off					0.37					0.78
No	78 (90.7)	55 (83.3)	23 (85.2)	31 (93.9)		98 (89.9)	81 (88.0)	37 (90.2)	32 (84.2)	
Yes	8 (9.3)	11 (16.7)	4 (14.8)	2 (6.1)		11 (10.1)	11 (12.0)	4 (9.8)	6 (15.8)	
Worried about being fired					0.08					0.001
No	82 (95.4)	57 (86.4)	24 (88.9)	27 (81.8)		106 (97.3)	83 (90.2)	41 (100)	30 (79.0)	
Yes	4 (4.7)	9 (13.6)	3 (11.1)	6 (18.2)		3 (2.8)	9 (9.8)	0 (0.0)	8 (21.1)	
Unemployed Women										
Looked for work in the past month					0.08					0.69
No	40 (100.0)	39 (97.5)	21 (100)	17 (89.5)		21 (95.5)	20 (90.9)	10 (83.3)	14 (87.5)	
Yes	0 (0.0)	1 (2.5)	0 (0.0)	2 (10.5)		1 (4.6)	2 (9.1)	2 (16.7)	2 (12.5)	

All *p* from Fisher's exact tests; N=Number; missing: look for work: 1 at 3 months, 1 at 12 months

<$50,000 was associated with a 2.23 times higher risk of losing income compared to income ≥ $50,000 (95% CI (1.04, 4.78)). Women with stage III disease had a 2.68 times higher risk of losing income than stage I disease with borderline statistical significance (95% CI (0.98, 7.37)). Women with baseline incomes <$50,000 compared to ≥ $50,000 were more likely to gain income (RR=8.47, 95% CI (3.87, 18.81)). Married women were more likely to gain or maintain income ≥ $100,000 than unmarried women (RR=3.76, 95% CI (1.50, 9.41); RR=2.56, 95% CI (1.08, 6.06); respectively). Similar results were seen when the models were adjusted using propensity score quintiles (Appendix 3.4), adjusted for 3-month employment, and when we used the change in income variable from the $25,000 range income categories (data not shown).

Women maintaining incomes ≥ $100,000 reported financial and insurance problems less frequently than women in the other income change categories (Table 3.3). Of women maintaining incomes ≥ $100,000, 5.3% at 3 months and 7.6% at 12 months reported financial problems, compared to 49.1% at 3 months and 56.4% at 12 months of women losing income (3 and 12-month p<0.0001).Women maintaining incomes ≥ $100,000 (3 month=3.0%, 12 month=5.3%) and women maintaining the same income <$100,000 (3 month=7.8%, 12 month=7.0%) reported insurance problems less frequently than women who gained (3 month=22.2%, 12 month=11.1%) or lost income (3 month=25.5%, 12 month=20.0%) (3 month: p<0.0001, 12 month: p=0.02).

The proportion of employed women was similar among income change categories (Table 3.3). Two women lost employment between the 3 and 12-month surveys, with 53 gaining employment, 210 remaining employed, and 66 remaining unemployed (Table 3.1). Among employed women, worries about discussing cancer with coworkers or taking time off work were

similar across income change categories. At 12 months, the percentage worried about being fired varied by income change (0% gaining income to 21% losing income, p=0.001).

DISCUSSION

In this study of young women with breast cancer, stress, anxiety and depression were not associated with changes in household income. However, our finding that lower income was associated with losing income suggests that these women may be more vulnerable to income loss, and clinicians of lower income women may want to proactively offer available resources to address financial needs.

Most QOL literature examines how the financial burden of cancer influences QOL, rather than looking at the impact that psychosocial factors can have on finances.[7,20,21] The amount of distress felt at diagnosis may impact how women balance treatment with work obligations, which in turn may affect income. However, stress, anxiety, and depression were not associated with losing or gaining income in this study, suggesting that the presence of these psychosocial factors may not create a burden large enough to impact household income. A review found that psychosocial factors such as depression and distress made it hard for women with breast cancer to return to work.[22] However, not returning to work may not be directly linked to changing incomes if her partner compensates for any lost income.

Partners may also face psychosocial and economic distress.[23-25] One study found that 32% of partners reduced working hours to help a partner though treatment and 32% reported a worse financial status.[10] Another study found that 5% of caregivers had to quit their job.[26] While our study did not specifically look at the partner, part of the financial loss seen among the participants may have resulted from the impact on the partners' ability to work

This study found that losing income was associated with lower baseline incomes and possibly more advanced disease. Women with high incomes may have more resources available that lessen the risk of losing income. A study using SEER found that women with incomes <$50,000 had 1.77 times higher odds of a worsening financial status due to breast cancer than women with incomes ≥ $50,000.[27] Additionally, 27% of women reported decreasing work hours due to cancer-related health issues.[27] Women with later stage disease, regardless of income, may find treatments particularly disruptive which may result in reduced work hours. However, like our results, the SEER study found that stage III vs. stage I disease was borderline associated with worsening financial statuses (OR=1.92, p=0.06).[27]

We also found that married women and those with lower incomes were more likely to gain income. Some women with lower incomes and/or their partners may have been students and their income may have increased upon graduation. Lower income women may have gained income if they increased work hours to cover costs or gain health insurance coverage. In our study, 22% of women gaining income reported insurance problems at 3 months. The SEER study found that 7% of women increased work hours to cover cancer-related medical expenses.[27] Interestingly, the group of women changing income levels, be it lost or gained, tended to have lower incomes. This may highlight that poorer women experience more volatility around cancer treatment, and more research looking at the reasons for these observations is needed.

One surprising finding was that only two women lost employment, while 53 women gained employment between 3 and 12 months. Other studies have reported that women stop working after a breast cancer diagnosis more frequently.[5,21] The difference in our findings may be due to the lack of baseline employment and student status data. We examined medical records for unemployed women and noted few changes in employment after diagnosis. Without large

amounts of unemployment, lost income may have been the result of reduced hours; however, data on hours worked was not collected. Additionally, we do not know if women who remained employed did so because they enjoyed their job or if they felt locked into their job and were afraid to change positions due to worries about insurance. We saw that employed women losing and maintaining the same income <$100,000 were most worried about being fired at 3 months.

Study Limitations

First, the relatively small number of women whose incomes changed limited the power of the analysis and the number of covariates we could adjust for. We performed a propensity score adjusted analysis adjusting for additional covariates and obtained similar results. Second, we only had categorical income information which limited our ability to track all income changes. We were unable to look at changes for women maintaining ≥ $100,000, so our results may not be generalizable to those women. Also, our main outcome was change in household income, but we did not collect information about the partner's employment.

Third, we were unable to adjust for potentially important confounders including social support and insurance status. If we had this information, we would expect the results to be lower in magnitude than what we saw, due to the inverse relationship between these variables and psychosocial measures as well as income change. Fourth, since the trial occurred from 2012-2014, the financial crisis in 2008 and the Affordable Care Act in 2010 may have impacted the insurance and income stability of participants. Fifth, all information was self-reported, so there could be misclassification of income and psychosocial measures. Nonetheless, we believe that any misclassification was non-differential. Lastly, women who participated in this trial may be different from the larger population of young breast cancer patients. While this is a national

sample recruited from both community and academic sites, women in this study may be more health conscious, and have better financial or personal resources.

Clinical Implications

Our study found that lower income breast cancer patients had a higher risk of losing income than women with higher incomes. This group of women may need more support during treatment and early survivorship. Further research to understand reasons for these associations and what can be done to help women at risk of losing income will be important to improving the care of young women with breast cancer.

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Appendix Table 3.1: Analysis by randomization arm (YWI vs PAI)

	Odds Ratio	(95% CI)	p value
Household Income			
Income Lost (vs gain or same)	0.79	(0.44, 1.41)	0.43
Income Gained (vs lost or same)	1.52	(0.85, 2.77)	0.16
Income Changed (vs same)	1.12	(0.71, 1.77)	0.62
Income Lost vs no change	0.85	(0.47, 1.53)	0.59
Income Gained vs no change	1.49	(0.82, 2.72)	0.19

Each row is a separate regression model, generalized estimating equations were used to account for within-cluster correlations, an exchangeable correlation structure was used, YWI = young women's intervention, PAI = physical activity intervention, CI = confidence interval

Appendix Table 3.2: Comparison of women included to women excluded

	Income information known (N=356) N. (%)	Income information not complete (N=58) N. (%)	p value
Demographics			
Age			0.04[a]
<35	76 (21.4)	5 (8.6)	
35-39	87 (24.4)	20 (34.5)	
40-45	193 (54.2)	33 (56.9)	
Education			0.02
≤High School	35 (9.8)	12 (20.7)	
≥Some College	321 (90.2)	46 (79.3)	
Married			0.52
Yes	288 (80.9)	49 (84.5)	
No	68 (19.1)	9 (15.5)	
Children			0.02
Yes	261 (73.5)	51 (87.9)	
No	94 (26.5)	7 (12.1)	
Race/Ethnicity			0.85
Non-Hispanic, White	272 (76.6)	43 (75.4)	
Minority	83 (23.4)	14 (24.6)	
Region			0.43
Northeast	91 (25.6)	14 (24.1)	
South and Southeast	92 (25.8)	13 (22.4)	
Midwest	117 (32.9)	25 (43.1)	
West	56 (15.7)	6 (10.3)	
Change in Employment			0.002[a]
None–Employed	210 (63.4)	23 (41.8)	
None–Unemployed	66 (19.9)	19 (34.6)	
Lost job	2 (0.6)	3 (5.5)	
Gained job	53 (16.0)	10 (18.2)	
Household Income			<0.0001[a]
<$50,000	92 (25.8)	9 (15.5)	
$50,000-$99,999	121 (24.0)	5 (8.6)	
≥$100,000	143 (40.2)	12 (20.7)	
Missing	0 (0.0)	32 (55.2)	
Cancer and Baseline Cancer Treatment			
Stage			0.52
I	127 (35.7)	20 (34.5)	
II	174 (48.9)	32 (55.2)	
III	55 (15.5)	6 (10.3)	
Estrogen Receptor			0.85
Positive	266 (74.7)	44 (75.9)	
Negative	90 (25.3)	14 (24.1)	
Progesterone Receptor			0.23
Positive	249 (69.9)	45 (77.6)	
Negative	107 (30.1)	13 (22.4)	
Her2			0.50
Positive	83 (23.5)	16 (27.6)	
Negative	270 (76.5)	42 (72.4)	

Appendix Table 3.2: Comparison of women included to women excluded (Continued)

	Income information known (N=356) N. (%)	**Income information not complete (N=58)** N. (%)	p value
Chemotherapy			0.44
Yes/Planned	289 (82.1)	50 (86.2)	
No	63 (17.9)	8 (13.8)	
Radiation			0.55
Yes/Planned	198 (67.6)	31 (63.3)	
No	95 (32.4)	18 (36.7)	
Endocrine Therapy			0.46
Yes/Planned	246 (74.6)	42 (79.3)	
No	84 (25.5)	11 (20.8)	
Baseline Psychosocial Measures			
Stress			0.84[a]
Low	124 (35.8)	21 (38.9)	
Moderate	198 (57.2)	29 (53.7)	
High	24 (6.9)	4 (7.4)	
Anxiety			0.88
Normal	144 (41.0)	25 (44.6)	
Borderline	87 (24.8)	13 (23.2)	
Anxiety	120 (34.2)	18 (32.1)	
Depression			0.60
No	198 (59.6)	33 (63.5)	
Yes	134 (40.4)	19 (36.5)	

([a])Fisher's exact test; N=Number; unknown values not shown: 1 children, 2 race/ethnicity, 28 employment, 3 HER2, 4 chemotherapy, 72 radiation, 31 endocrine therapy, 14 stress, 7 anxiety, 30 depression; 100% of women had/planned surgery

Appendix Table 3.3: Amount of change in household income by income at baseline

	Change in Household Income	
	Loss (N=55)	**Gained (N=54)**
Amount Gained or Loss	N. (%)	N. (%)
All Incomes		
$20,001 or more	27 (49.1)	27 (50.0)
$10,001 to $20,000	17 (30.9)	19 (35.2)
$5,001 to $10,000	11 (20.0)	8 (14.8)
Incomes <$25,000 at baseline		
$20,001 or more	-	6 (35.3)
$10,001 to $20,000	2 (2.0.0)	3 (17.7)
$5,001 to $10,000	8 (80.0)	8 (47.1)
Incomes $25,000-$49,999 at baseline		
$20,001 or more	4 (30.8)	4 (20.0)
$10,001 to $20,000	6 (46.2)	16 (80.0)
$5,001 to $10,000	3 (23.1)	-
Incomes $50,000-$74,999 at baseline		
$20,001 or more	1 (10.0)	10 (100.0)
$10,001 to $20,000	9 (90.0)	-
$5,001 to $10,000	-	-
Incomes $75,000-$99,999 at baseline		
$20,001 or more	11 (100.0)	7 (100.0)
$10,001 to $20,000	-	-
$5,001 to $10,000	-	-
Incomes ≥ $100,000 at baseline		
$20,001 or more	11 (100.0)	-
$10,001 to $20,000	-	-
$5,001 to $10,000	-	-

To calculate the amount in the change in income the average of each income category was chosen for the value used in the subtraction of (income at 12 months – income at baseline), for incomes $100,000+ the value $125,000 was assigned, N = number, values not shown were unable to be determined from the dataset due to the categories used

Appendix Table 3.4: Comparison of multinomial logistic regression model to the propensity score adjusted logistic regression model for the impact of stress, depression, and anxiety at baseline on changing household income vs maintaining same household income <$100,000

	Multinomial Logistic Regression				Propensity Score Adjusted Logistic Regression			
	Lose Income		Gain Income		Lose Income		Gain Income	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
Stress								
Low	Ref.		Ref.		Ref.		Ref.	
Moderate or High	1.48 (0.70, 3.11)	0.30	1.02 (0.46, 2.23)	0.97	1.45 (0.69, 3.05)	0.33	1.15 (0.56, 2.38)	0.70
Depression								
No	Ref.		Ref.		Ref.		Ref.	
Yes	1.41 (0.70, 2.85)	0.34	0.90 (0.42, 1.93)	0.78	1.43 (0.70, 2.99)	0.32	0.91 (0.44, 1.87)	0.80
Anxiety								
Normal	Ref.		Ref.		Ref.		Ref.	
Borderline or Anxious	1.14 (0.57, 2.28)	0.71	1.21 (0.57, 2.56)	0.62	1.20 (0.60, 2.41)	0.60	1.36 (0.68, 2.73)	0.38

Separate regressions were run for stress, depression and anxiety (each row); the reference category for the multinomial logistic regression is same income <$100,000; the multinomial logistic regression was adjusted for age (continuous), cancer stage, marital status, children, race/ethnicity, and baseline income; the propensity score was created by using a logistic regression to predict each dichotomized exposure status separately, the propensity score model included the variables age (categorical), marital status, race/ethnicity, children, income at baseline, cancer stage, chemotherapy at baseline, and type of medical practice (academic vs. community), the propensity score was split into quintiles and added as a covariate to the multinomial logistic regression; each row is a separate regression model; RR= Risk Ratio; CI = Confidence Interval