Effects of Direct-to-Consumer Advertising and Clinical Guidelines on Appropriate Use of Human Papillomavirus DNA Tests

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Background: Both clinical guidelines and direct-to-consumer (DTC) advertising influence the use of new health care technologies, but little is known about their relative effects. The introduction of a cervical cancer screening test in 2000 offered a unique opportunity to assess the 2 strategies.

Objective: To evaluate the effects of clinical guidelines and a targeted DTC advertising campaign on overall and appropriate use of human papillomavirus (HPV) DNA tests.

Research Design: Quasi-experimental study using difference-in-differences analysis. Data were MarketScan private insurance claims for 500,000 women aged 21 to 64 enrolled at least 12 consecutive months from January 2001 through December 2005.

Results: Both clinical guidelines and DTC advertising were associated with increases in overall HPV DNA test use. DTC advertising was associated with a statistically significant increase in HPV DNA test use in 2 groups of DTC cities (+5.57%, $P < 0.0001$; +2.54%, $P < 0.0001$). DTC advertising was associated with comparable increases in the probability of appropriate and inappropriate use of the HPV DNA test in primary screening. Clinical guideline releases from the American College of Obstetricians and Gynecologists, and by a cosponsored panel, were associated with greater increases in HPV DNA tests for appropriate primary screening than for inappropriate primary screening ($\beta = 0.3347$, $P < 0.05$ and $\beta = 0.4175$, $P < 0.01$).

Conclusions: DTC advertising was associated with increased overall use of a cervical cancer screening test, whereas clinical guidelines were differentially associated with increased appropriate use. These findings suggest distinct influences of consumer marketing and professional guidelines on the use of health care products and services.

Key Words: clinical guidelines, consumer marketing, appropriate use, medical technologies

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It is now widely recognized that prescription drugs, medical procedures, and diagnostic tests are often underused, overused, or misused.[1] Payers, regulators, and professional groups favor clinical guidelines as a means of disseminating information about appropriate use of health care technologies,[2] but adherence to guidelines is often poor.[3] Direct-to-consumer (DTC) advertising is an increasingly common strategy for pharmaceutical manufacturers interested in promoting use of their products.[4] Although manufacturers argue that DTC advertising increases the likelihood that patients receive appropriate care for underdiagnosed and undertreated conditions,[5] others have expressed concern that DTC advertising may increase unnecessary and inappropriate care.[6]

The increasing use of the human papillomavirus (HPV) DNA test for cervical cancer screening offers a unique opportunity to examine the roles and relative effects of clinical guidelines and DTC advertising. Cervical cancer screening is a rich context for investigating patterns and predictors of appropriate use, as both underuse and overuse of screening tests have been documented in different groups.[7,8]

Between April 2002 and February 2004, 5 sets of cervical cancer screening guidelines were released by professional associations and consensus groups.[9–13] With the exception of guidelines from the US Preventive Services Task Force, which cited insufficient evidence to recommend for or against routine screening for HPV infection,[9] the guidelines generally agree that HPV DNA testing is one option for follow-up of equivocal Papanicolaou test results, known as atypical squamous cells of uncertain significance (ASC-US), and for use in primary screening among women age ≥30 in conjunction with a Papanicolau test. Guidelines from the American College of Obstetrics and Gynecology (ACOG) recommend that (*a*) HPV DNA tests be used for follow-up of Papanicolau test results deemed ASC-US, regardless of the woman's age, and (*b*) it is appropriate to administer HPV

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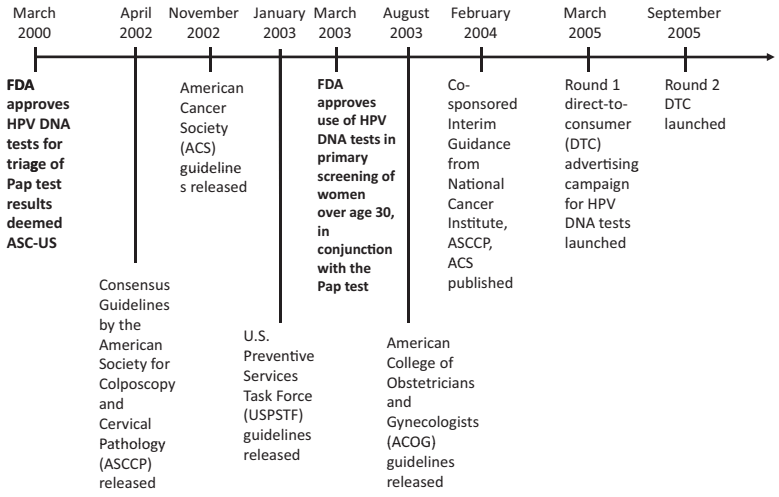

FIGURE 1. Timeline of FDA approvals, clinical guideline releases, and DTC advertising launches for HPV DNA tests.

DNA tests at the same time as a Papanicolau test for women aged 30 and older.[11] Interim guidance released in February 2004 by a consensus panel of the American Society of Colposcopy and Cervical Pathology and the American Cancer Society concurred that the HPV DNA test may be added to cervical screening for women age 30 and older.[13] In March 2005, the HPV DNA test manufacturer, QIAGEN (formerly Digene Corporation), initiated a targeted DTC advertising campaign.

The present study aimed to assess the effects of a DTC advertising campaign on use of HPV DNA tests; to estimate how much of the observed increase in HPV DNA testing is attributable to appropriate versus inappropriate use; and to evaluate the relative effects of the DTC campaign and clinical guidelines on appropriate use.

METHODS

We used difference-in-differences analysis to control for secular trends in the use of HPV DNA tests (ie, use not associated with the DTC campaign). We compared HPV DNA test use in markets where there was DTC advertising with use in a set of comparison markets where there was no DTC advertising, before and after the advertising periods. The differences-in-differences approach assumes that the secular trends across markets were similar in the pre-DTC advertising period. We assessed the comparability of DTC and comparison markets by comparing pre-DTC advertising trends in use of HPV DNA tests.

HPV DNA Test Approvals

The HPV DNA test was first approved by the Food and Drug Administration (FDA) in 2000 for follow-up of ASC-US Papanicolau test results (Fig. 1). In March 2003, the FDA approved a second indicated use, primary screening in women over age 30, in conjunction with a Pap test[14]; this indication substantially expanded the potential market for the test. Primary screening in women less than 30 years is not recommended because there is a high prevalence of spontaneously resolving transient HPV infections among younger women.[13]

DTC Advertising Campaign

The QIAGEN DTC advertising campaign consisted of print advertisements in national women's magazines, and television advertisements in urban markets for 3-month periods. The print advertisements established low-level exposure to advertising messages across the country; our study investigates the effect of the television advertisements, which were targeted to specific cities. The initial round of television advertisements was broadcast between March and May 2005 in the Atlanta, Baltimore, and Philadelphia areas. A second round of advertisement was broadcast from September through November 2005 in the Boston and Chicago areas. Television advertisements were also broadcast in subsequent years; this study examines the first year of the campaign only.

Comparison Markets

We selected 2 sets of cities as potential comparison groups, applying different criteria to identify cities similar to those targeted by QIAGEN′s DTC campaign during the study period.

Comparison Group 1

Drug manufacturers often select DTC cities on the basis of characteristics, such as sales force presence, which are not readily observable. For the first set of comparison cities, we selected cities that were most likely to share these unobservable characteristics: 10 cities in which QIAGEN broadcast DTC advertisements in 2006 and the first half of 2007 (ie, after the study period). These cities are Dallas, TX; Houston, TX; Los Angeles, CA; Miami, FL; New York, NY; Orlando, FL; Pittsburgh, PA; San Francisco, CA; Tampa, FL; and Washington, DC.

Comparison Group 2

QIAGEN′s media plan for 2005 through 2008 targeted cities that are among the most populous in the United States. Our second set of comparison cities consisted of 10 cities of similar size: the 10 most populous cities in the United States in which QIAGEN DTC advertisements were not broadcast in 2005 or the first half of 2006. These cities are Austin, TX;

Charlotte, NC; Columbus, OH; Indianapolis, IN; Jacksonville, FL; Los Angeles, CA; Memphis, TN; Phoenix, AZ; San Antonio, TX; and San Diego, CA.

Areas for the DTC and comparison cities were defined according to Designated Market Areas, groups of counties that are covered by specific groups of television stations, and used by media planners to purchase advertising time.[15]

To assess the comparability of campaign and comparison areas for each round of the DTC campaign, we calculated the monthly difference in HPV DNA test use between DTC and comparison group cities, and tested the significance of these differences over the pre-DTC advertising period using linear regression.

Data

Data on HPV test use were from the Medstat Group's MarketScan database, which contains linked enrollment and medical claims data for 29 million beneficiaries insured through 77 employers.[16] To restrict the data to a manageable size for analysis, we randomly selected 500,000 female patients aged between 21 and 64 years. We excluded women who had a hysterectomy during the study period. To allow for adequate assessments of cervical screening and follow-up, only those participants enrolled for at least 12 consecutive months were included.

The timing and location of DTC promotions were determined by reviewing QIAGEN′s internal marketing documents.

Measures

We identified HPV DNA test use with Current Procedural Terminology codes, 87620, 87621, 87622. HPV DNA tests were deemed "appropriate" for use in primary screening if they were claimed for women age 30 and older. Tests were deemed "inappropriate" for use in primary screening if they were claimed for women age less than 30, in the absence of an ASC-US diagnosis code (International Classification of Diseases, Ninth Revision, Clinical Modification code 795.01). As the QIAGEN DTC campaign messages were designed to promote the use of HPV DNA tests in primary screening, the appropriate use analysis focuses on primary screening, and excludes appropriate use for the purpose of ASC-US triage.

The independent variables of interest in the study were as follows: (*a*) residence in one of the DTC or comparison city metropolitan areas, (*b*) whether the period was before or after DTC advertisements were broadcast, and (*c*) whether the period was before or after clinical guidelines were released. Residence in a DTC or comparison metropolitan area was determined according to the enrollee's county FIPS code.

Other independent variables were patient age, ASC-US diagnosis, urban/rural residence (population of 20,000 or more, or less than 20,000), region of residence (Northeast, North Central, South, or West), type of private insurance (comprehensive, exclusive provider organization or preferred provider organization, health maintenance organization or point-of-service with capitation, point-of-service, consumer-driven health plan), total months of enrollment, specialty of the provider submitting the screening test claim or claim for the most recent clinical visit (primary care provider, obstetrician/gynecologist, pathologist, or other), number of months since the beginning of the study period, and occurrence of FDA approvals and clinical guideline releases.

Analysis

We estimated the effects of the DTC campaign using the difference-in-differences method. The difference-in-differences is the average difference in HPV test use that would be expected to be observed because of the underlying time trend subtracted from the average difference in HPV test use from before the DTC campaign to after its initiation. This method allows us to account for secular trends in HPV DNA test use, and to attribute any remaining differences in HPV DNA test use to the effects of the DTC campaign.

For the analysis of the effects of DTC advertising on overall HPV test use, the difference-in-differences is the average difference (before and after the initiation of the DTC campaign) in HPV DNA test use in comparison cities subtracted from the average difference before and after the DTC campaign in DTC cities. The time frame for this analysis was between January 2001 and December 2005.

For the analysis of the effects of DTC advertising on appropriate HPV test use in primary screening, the difference-in-differences is the average difference in HPV test use for primary screening among women age 30 and older (ie, appropriate use) from before the DTC campaign to after its initiation subtracted from the average difference in HPV test use for primary screening among women under age 30 (ie, inappropriate use) from before the DTC campaign to after its initiation. Women with an ASC-US diagnosis were excluded. The time frame for analysis of primary screening was from March 2003, the date of FDA approval of that indication, through the end of the study period, December 2005.

To account for correlation between multiple tests received by the same woman over time, associations between predictors and HPV DNA test use were estimated using generalized estimating equations, assuming an exchangeable correlation matrix structure.[17] Alternative matrix structures were tested, and results were consistent. Because the logistic model is nonlinear, the net effect of the DTC campaign on HPV test use cannot be calculated directly from the coefficient of the interaction term[18]; therefore, we calculated the average effect on the probability of HPV test use by using simulation methods based on the estimated models. We used bootstrap samples to construct 95% confidence intervals for our final estimates.[19] Statistical analyses were conducted with SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

The DTC cities and the matched groups of comparison cities were comparable in their HPV DNA test use trends before the introduction of DTC advertising, satisfying the primary assumption of the difference-in-differences method (Fig. 2). Differences between HPV DNA test use trends before the introduction of DTC advertising in the Comparison Group 1 and Round 1 DTC cities, and between Comparison Group 2 and Round 2 DTC cities, were not significant at $P < 0.05$.

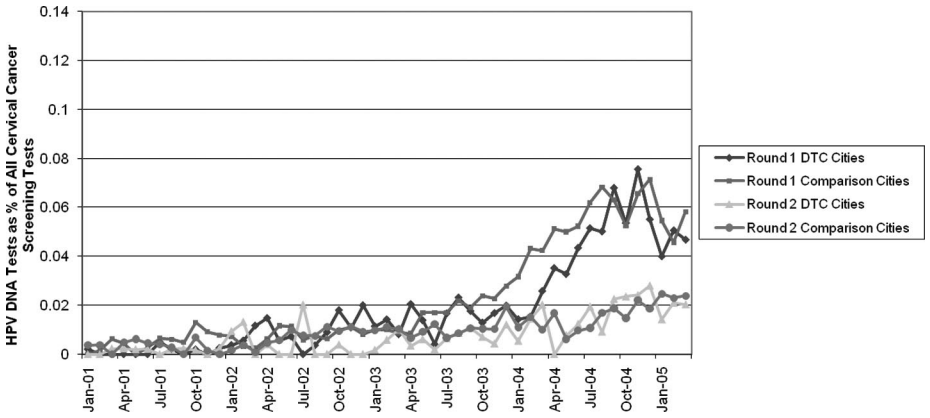

FIGURE 2. Actual HPV DNA test use, as a proportion of all cervical cancer screening tests, in DTC and comparison cities in the pre-DTC period, January 2001 through February 2005.

TABLE 1. Predicted Probability of HPV DNA Test Use

Metropolitan Area	Predicted Probability of HPV Test Use (%)		Change in Predicted Probability of HPV Test Use Before and After DTC Campaign (%)
	Before DTC	After DTC	
Round 1 DTC (March–May 2005)			
DTC cities (Atlanta, Baltimore, and Philadelphia)	2.34	10.36	5.57 (5.17, 5.98)*
Comparison group A cities†	2.70	5.15	
Round 2 DTC (September–November 2005)			
DTC cities (Boston and Chicago)	1.08	5.49	2.54 (1.86, 3.46)*
Comparison group B cities†	1.63	3.50	

Model contains variables for time trend, important dates, age, ASC-US diagnosis, urban residence, region of residence, insurance plan type, provider specialty, and months of enrollment. Difference-in-differences analysis was used to control for secular trends.

*$P < 0.0001$.

†Comparison cities for round 1 are Dallas, Houston, Los Angeles, Miami, New York, Orlando, Pittsburgh, San Francisco, Tampa, and Washington, DC. Comparison cities for round 2 are Austin, Charlotte, Columbus, Indianapolis, Jacksonville, Los Angeles, Memphis, Phoenix, San Antonio, and San Diego.

DTC indicates direct-to-consumer; HPV, human papillomavirus; ACS-US, atypical squamous cells of uncertain significance.

Type of insurance coverage differed significantly for women in the DTC and comparison cities; fewer than one-third of those in Round 1 and Round 2 DTC cities were covered by health maintenance organizations or point-of-service with capitation (30.4% and 24.0%, respectively), whereas 47.0% and 42.6% of women in Comparison Groups 1 and 2 were covered by such insurance (Appendix, Table 1, Supplemental Digital Content 1, available at: http://links.lww.com/MLR/A133).

Overall HPV DNA Test Use

Table 1 presents difference-in-differences estimates for the probability of HPV DNA test use in DTC and control cities, controlling for secular trends in the use of the test, and controlling for patient age, ASC-US diagnosis, urban residence, region of residence, insurance plan type, and provider specialty. There was a positive and significant effect of the DTC campaign in both Round 1 and Round 2 cities. The increase in HPV DNA test use in Round 1 cities was 5.57 percentage points greater than the increase in the control cities ($P < 0.0001$); the increase in HPV DNA test use in Round 2 cities was 2.54 percentage points greater than the increase in control cities ($P < 0.0001$). Figure 3 shows the predicted probability of HPV test use among residents of DTC Round 1 cities, DTC Round 2 cities, and comparison cities throughout the study period.

Clinical guidelines released by American Society of Colposcopy and Cervical Pathology and ACOG, cosponsored interim guidance, and the expanded FDA approval were all significantly associated with increases in the use of HPV DNA tests, above and beyond the secular time trend (Appendix, Table 2, Supplemental Digital Content 2, online only, available at: http://links.lww.com/MLR/A134). Accounting for the effects of DTC advertising, women living in urban areas, and those on HMO health plans were significantly more likely to receive HPV DNA tests than those living in rural or suburban areas, or those on comprehensive, PPO, or POS plans. Obstetrician/gynecologists were significantly more likely than primary care providers to administer HPV DNA tests.

Appropriate HPV DNA Test Use in Primary Screening

Table 2 reports difference-in-differences estimates for the probability of HPV DNA test use in primary screening among women age 30 and older (appropriate use) and women age 21 to 29 (inappropriate use), accounting for secular trends in the use of the test, and controlling for urban residence,

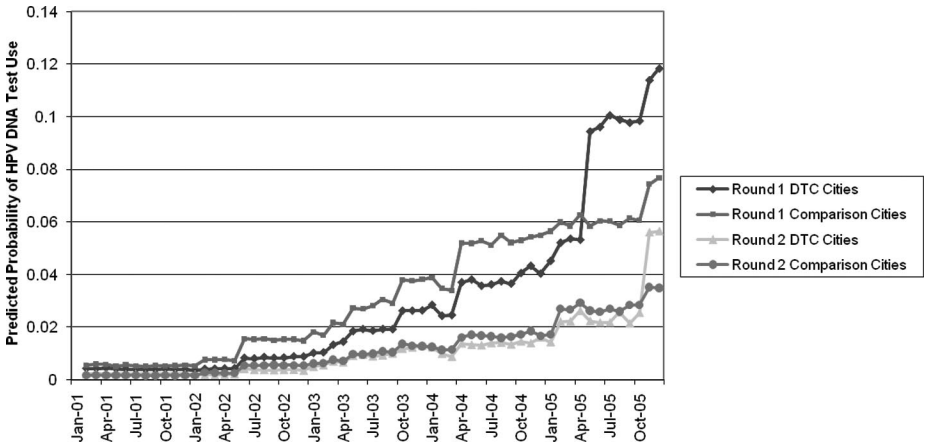

FIGURE 3. Predicted probability of HPV DNA test use given any cervical screening test in DTC and comparison cities, January 2001 to December 2005, controlling for time trend, dates of clinical guideline releases and DTC advertising launches, age, ACS-US, urban residence, region of residence, insurance plan type, provider specialty, and months of enrollment.

TABLE 2. Predicted Probability of HPV DNA Test Use in Primary Screening, by Age

Metropolitan Area	Predicted Probability of HPV Test Use in Primary Screening (%)		Change in Predicted Probability of HPV Test Use Before and After DTC Campaign (%)
	Before DTC	After DTC	
Age 30+ (appropriate)			
Round 1 DTC (March–May 2005)			
DTC cities (Atlanta, Baltimore, and Philadelphia)	3.60	10.40	5.44 (5.07, 5.83)*
Comparison group A cities†	3.81	5.17	
Round 2 DTC (September–November 2005)			
DTC cities (Boston and Chicago)	1.43	5.20	2.52 (1.77, 3.45)
Comparison group B cities†	1.83	3.08	
Age 21–29 (inappropriate)			
Round 1 DTC (March–May 2005)			
DTC cities (Atlanta, Baltimore, and Philadelphia)	2.34	6.00	3.32 (2.69, 4.06)*
Comparison group A cities†	2.86	3.20	
Round 2 DTC (September–November 2005)			
DTC cities (Boston and Chicago)	1.30	3.41	1.03 (−0.02, 4.06)
Comparison group B cities†	1.39	2.47	

Model contains variables for time trend, important dates, age, ASC-US diagnosis, urban residence, region of residence, insurance plan type, provider specialty, and months of enrollment. Difference-in-differences analysis was used to control for secular trends.

*$P < 0.01$.

†Comparison cities for round 1 are Dallas, Houston, Los Angeles, Miami, New York, Orlando, Pittsburgh, San Francisco, Tampa, and Washington, DC. Comparison cities for round 2 are Austin, Charlotte, Columbus, Indianapolis, Jacksonville, Los Angeles, Memphis, Phoenix, San Antonio, and San Diego.

DTC indicates direct-to-consumer; HPV, human papillomavirus; ACS-US, atypical squamous cells of uncertain significance.

region of residence, insurance plan type, and provider specialty. Increases in primary screening were significantly greater in Round 1 cities than in control cities for both age groups of women; however, there were not significant increases related to DTC advertising in Round 2 cities for either age group of women. In Round 1 DTC cities, the increase in appropriate primary screening among women aged 30 and older was 5.44% greater than the increase in the control cities; the increase in inappropriate primary screening among younger women was 3.32% greater than the increase in control cities.

Round 1 of the DTC campaign was associated with a significant increase in HPV DNA test use in primary screening for both women age 30 and older and women age 21 to 29. A 3-way interaction term between age, DTC location, and DTC date was not statistically significant, indicating that the increase in HPV DNA test use for primary screening was not different across age groups (Appendix, Table 3, Supplemental Digital Content 2, available at: http://links.lww.com/MLR/A135). That is, Round 1 DTC advertising was related to comparable increases in the probability of appropriate and inappropriate use of the HPV DNA test in primary screening.

Two-way interaction terms between age and the dates of each set of clinical guideline releases were statistically significant, suggesting that the releases of ACOG guidelines and cosponsored interim guidance were associated with greater increases in HPV DNA tests for appropriate primary screening (among women age 30 and older) than inappropriate primary screening (among women younger than age 30) (Appendix, Table 3, Supplemental Digital Content 2, available at: http://links.lww.com/MLR/A135).

DISCUSSION

DTC advertising was associated with an increase in use of HPV DNA tests, but did not promote targeted use of the test in primary screening among age groups of women specified by clinical guidelines. This result is consistent with previous evaluations of DTC advertising, which have found that patients who make a request for advertised COX-2 inhibitors or antidepressants are more likely to receive a prescription than those who do not make a request, regardless of whether the request is in keeping with clinical guidelines.[20,21]

The consequences of inappropriate use of advertised health products and services include excess costs, side effects, and adverse events resulting from unnecessary use. The desirable balance of appropriate and inappropriate use may vary, according to the costs and benefits associated with each. For example, 1 study of DTC advertising for antidepressants estimated that whereas most antidepressant prescriptions driven by DTC advertisements are written for nondepressed patients, the economic costs of treating these patients may be outweighed by the large benefit of treating a small number of depressed patients who would otherwise have gone untreated.[22] On the other hand, treating patients with a newer, more expensive advertised agent that is a substitute for an existing, inexpensive alternative may present excess costs that are much greater than the product's marginal benefits in efficacy or acceptability.

To realize the potential of DTC advertising with minimal increases in inappropriate use, approaches that target both patients and physicians may be needed. At present, most DTC television advertisements do not effectively convey that the advertised product is not suitable for everyone, and consumers are unable to answer basic questions about much of the content of DTC television ads.[23] The appropriateness of patient inquiries may be increased through improved clarity and completeness of advertising; for example, drug facts boxes in advertisements have been shown to increase consumers understanding of prescription drug benefits and side effects.[24]

Physicians frequently accommodate patient requests for advertised drugs and services, even when fulfilling requests does not result in superior care.[25,26] However, our study found that clinical guideline releases were associated with greater increases in appropriate use than in inappropriate use, suggesting that guidelines have the potential to affect clinicians' practices appropriately, even in the context of product marketing.

The effect of guidelines on appropriate use could be optimized at the stages of both guideline development and dissemination. Consideration of expected marketing messages during the guideline development process may help guidelines anticipate the content and prevalence of patient requests. Implementation of proven interventions, such as audit and feedback, reminder systems, and academic detailing, upon the release of new clinical guidelines may help to maximize the degree to which advertising-driven patient requests result in appropriate use of new technologies.[3]

Most evaluations of DTC advertising assess the effect of large-scale nationwide campaigns that begin concurrently with a product's market entry. Such studies are limited in their ability to make causal inferences, as precampaign usage data are unavailable, and control groups are exposed to at least some DTC advertising. Our study evaluated a DTC campaign that began 5 years after the initial FDA approval of the advertised product, and that targeted advertisements to local markets over discrete periods. These unique features allowed us to control for preadvertising trends, and to evaluate DTC advertising effects by comparing locations exposed to DTC advertisements with comparable unexposed locations.

Our study has several limitations. As in all difference-in-differences analyses, there is a chance that concurrent alternative influences were responsible for the effects we attribute to the interventions; however, the similarity of the increases in HPV DNA test use across 2 sets of intervention and control groups reduces the likelihood that alternative explanations were responsible for the effects we observe. We are aware of no other relevant events, such as changes in insurance coverage or publication of influential research, which occurred concurrently with the 2 rounds of the DTC campaign under study. In addition, it is possible that although the DTC and comparison cities had comparable pretrends in HPV DNA test use, they differed in unmeasured ways that may have influenced adoption of HPV DNA tests.

Our data do not allow us to identify socioeconomic or other characteristics that may influence women's likelihood of being exposed to advertisements, or to determine whether women who received HPV DNA tests saw the advertisements. However, DTC campaigns may influence health care providers or provider groups to change their practice norms, regardless of whether individual patients are exposed to DTC advertisements. Our understanding from a QIAGEN marketing representative is that all DTC cities were targeted with provider-side sales force visits, as well. This limits our ability to disentangle the effects of DTC advertising from the physician promotions reinforcing it. As virtually all DTC campaigns are complemented by a diverse marketing plan that includes physician detailing and advertisements, we believe that our study represents an accurate picture of the effects of a DTC campaign that includes these supporting elements.

We also did not have any information on the reasons why providers administered seemingly inappropriate HPV DNA tests to women under age 30. Because we used consistent definitions throughout the study period, findings on relative changes in appropriate and inappropriate use should not be biased.

Because market regions may overlap slightly, and because broadcast television stations sell their content for rebroadcast by satellite and cable companies, regionally targeted advertisements may have been viewed in other parts of the country. This may have resulted in a small amount of contamination in our comparison cities, thereby causing us to underestimate the effects of DTC advertising on HPV DNA test use. Therefore, our results may be conservative estimates of the effect of DTC advertising.

Finally, our study of privately insured women cannot provide insight into whether DTC advertising increases utilization among those who need it most. Survey data suggest that those with lower household income and education are less likely to see DTC advertising than those with higher incomes or more education.[27] Further research is required to explore whether the effects of DTC promotions reach and influence these underserved populations, which are not typically the primary targets of marketing campaigns.

The results of this study suggest that DTC advertising may be an effective way of increasing use of cancer screening or other health care technologies, but that these increases may be composed of some inappropriate use. Importantly, our results also highlight the ability of clinical guidelines to improve the balance of appropriateness by channeling use to target populations. Together, these findings suggest distinct influences of consumer marketing and professional guidelines on use of health care products and services.

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