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The association between cigarette smoking, cancer screening, and cancer stage: A prospective study of the Women's Health Initiative Observational Cohort

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KEYWORDS

Smoking Status

Cancer Screening

Cancer Stage

Breast Cancer

Cervical Cancer

Colorectal Cancer

ABSTRACT

Objective

To assess the dose-dependent relationship between smoking history and cancer screening rates or staging of cancer diagnoses.

Design

Prospective, population-based cohort study

Setting

Questionnaire responses from the Women's Health Initiative (WHI) Observational Study

Participants

89,058 postmenopausal women

Outcome Measures

Logistic regression models were used to assess the odds of obtaining breast, cervical, and colorectal cancer screening as stratified by smoking status. The odds of early-stage and late-stage cancer diagnoses among patients with inadequate screening were also calculated.

Results

Over an average of 8.8 years of follow-up, current smokers had lower odds of obtaining breast (OR 0.49; 95% CI: 0.51-0.59), cervical (OR 0.53; 95% CI: 0.47-0.59), and colorectal cancer (OR 0.71; 95% CI: 0.66-0.76) screening. Former smokers were more likely than never smokers to receive regular screening services. Failure to adhere to screening guidelines resulted in diagnoses at higher cancer stages among current smokers for breast cancer (OR 2.78; 95% CI: 1.64-4.70) and colorectal cancer (OR 2.2556; 95% CI: 1.01 - 5.05).

Conclusions

Active smoking is strongly associated with decreased utilization of cancer screening services and more advanced cancer stage at the time of diagnosis. Clinicians should emphasize the promotion of both smoking cessation and cancer screening for this high-risk group.

ARTICLE SUMMARY

Strengths and limitations of this study

- This study utilizes prospective data drawn from a national cohort of nearly 90,000 postmenopausal women with 8.8 years of follow-up and annual central adjudication of cancer cases.
- There is a possibility of recall bias due to the use of self-reported questionnaire responses; however, meta-analysis has found the validity and accuracy of self-reported data to be high.

INTRODUCTION

Cigarette smoking is the single largest cause of cancer worldwide yet tobacco use is decreasing less rapidly in women than men, and lung cancer remains the leading cause of cancer death in women.[1,2] Data from mostly cross-sectional studies suggests that cancer screening services are underutilized in women, but other studies reported no association between smoking status and cancer screening; thus, additional research employing prospective follow-up could shed light on the relationship.[3] Because cigarette smoking is associated with other lifestyle risk factors, smoking status may also be associated with later stages of cancer presentation if healthcare is underutilized in this population.[4]

The Women's Health Initiative-Observational Cohort (WHI-OS) provides a unique opportunity to examine smoking as a barrier to cancer screening in a large, national cohort of multi-ethnic post-menopausal women. The present cross-sectional study will investigate use of cancer screening by smoking status, and determine whether a relationship between smoking and cancer screening is associated with the stage at cancer diagnosis among a nationally representative sample of women from the Women's Health Initiative-Observational Cohort (WHI-OS). We hypothesize that WHI-OS participants with history of smoking will have reduced use of cancer screening services and will have more advanced cancer stages at diagnosis. If smoking is associated with reduced cancer screening and more advanced cancer stages at diagnosis, then education and counseling interventions on the importance of cancer screening should be targeted to this high-risk group of individuals.

METHODS

Study Population - Women's Health Initiative

The Women's Health Initiative Observational Cohort recruited postmenopausal women from 40 clinical centers across the United States from October 1, 1993 to December 31, 1998. All WHI-OS participants had a physical examination at baseline and 3 years. Longitudinal data including demographics, risk exposures, health behaviors, and medical history were prospectively collected with annual mailed questionnaires. A central coordinating center established standardized data collection and reporting protocols for all study sites.[5] For this study, women with a diagnosis of cancer prior to or during the first year of the study were excluded from the analysis. Participants with unstaged cancers were also excluded.

Definition of Exposures

Smoking status was defined from a self-reported questionnaire administered at study entry. Participants were classified as smokers if they answer 'Yes' to the question "During your entire life, have you smoked at least 100 cigarettes?" Smokers were further classified as current smokers or former smokers. Current and former smokers were then classified based on frequency, amount, and duration of smoking.

Definition of Cases

The primary outcome was cancer screening (yes vs. no) as determined by baseline self-reported receipt of mammogram, Papanicolaou/"Pap" test, fecal occult blood test (FOBT), sigmoidoscopy, and colonoscopy. Lung cancer screening using low-dose computed tomography

was not yet available or recommended at the time of baseline assessments, so was not available for inclusion in our analyses.

The secondary outcome was cancer stage at diagnosis as determined by the Surveillance Epidemiology and End Results (SEER) 1988 classification method. Cancer outcomes were identified by an annual self-report questionnaire and centrally adjudicated by tumor registry coders. All *in situ* and localized cancers were classified as early stage cancers. Regional and distant cancers were classified as late stage cancers. Although breast, colorectal and cervical cancer are included in the screening analysis, only women diagnosed with incident breast and colorectal cancer were analyzed for cancer stage at presentation due to the small number of cervical cancer cases in the WHI-OS.

Statistical Analysis

Independent associations between smoking status and receipt of screening were investigated using separate multivariable logistic regression analyses with 95% confidence intervals (CIs) using never-smokers as the reference group within each table column. The following baseline covariates were accounted for in the statistical model: age, race/ethnicity, BMI, education, insurance type, usual care provider visit, and family history.

For cancer staging analysis, logistic regression models included all known cancer risk factors excluding smoking. Breast cancer covariates were based on the Gail model risk factors: sociodemographic characteristics, breast biopsy, family history of breast cancer, BMI, age at first birth, number of children breastfed, parity, and insurance type.[6] The colorectal model was

adjusted for sociodemographic characteristics, insurance type, BMI, family history of colorectal cancer, aspirin use, and alcohol consumption.[7]

Smoking status ('Never', 'Former', 'Current') was the primary exposure of interest and all other analyses were considered of secondary interest. Secondary analyses were adjusted for multiple comparisons using the Bonferroni correction method. All tests were two-sided and tested at the 0.05 level of significance.

RESULTS

A total of 89,058 women were included in the analysis of which 47,021 were never-smokers, 36,360 were former smokers, and 5,677 were current smokers. From study enrollment in 1993 until data retrieval in 2017, patients were followed for a median of 8.8 years. Nearly all of never smokers (99.88%) remained never smokers, and former smokers (98.97%) remained former smokers. 49.49% of current smokers at baseline were no longer smoking by the last data collection. There were 7,054 incident cases of breast cancer, 1,600 incident cases of colorectal cancer, and 61 incident cases of cervical cancer.

Table 1: OR and 95% CIs of Reporting Cancer Screening by Smoking Status

	Mammogram within the last 2 years OR (95% CI)*	**Pap smear within last 3 years OR (95% CI)***	**Colorectal screening within last 5 years OR (95% CI)***
Smoking status			
Never smoker	Ref	Ref	Ref
Current smoker	0.55 (0.51 - 0.59)	0.53 (0.47 - 0.59)	0.71 (0.66 - 0.76)
Former Smoker	1.05 (1.004 - 1.10)	1.10 (1.02 - 1.18)	1.03 (0.99 - 1.07)
Cigarettes per day			
Never smoker	Ref	Ref	Ref
Former			
<15	1.1 (1.04 - 1.16)	1.11 (1.01 - 1.21)	1.05 (0.998 - 1.1)
15-24	1.02 (0.95 - 1.1)	1.09 (0.97 - 1.22)	1.01 (0.95 - 1.07)
≥ 25	0.94 (0.86 - 1.01)	0.99 (0.87 - 1.13)	1.01 (0.94 - 1.08)
Current			
<15	0.63 (0.57 - 0.69)	0.58 (0.5 - 0.68)	0.78 (0.71 - 0.86)
15-24	0.47 (0.42 - 0.53)	0.53 (0.44 - 0.64)	0.63 (0.56 - 0.71)
≥ 25	0.49 (0.42 - 0.59)	0.37 (0.29 - 0.48)	0.65 (0.55 - 0.78)
Pack-years			

Never smoker	Ref	Ref	Ref
Former			
<20	1.11 (1.05 - 1.17)	1.13 (1.03 - 1.23)	1.04 (0.99 - 1.09)
≥ 20	0.96 (0.9 - 1.02)	0.99 (0.90 - 1.10)	1.02 (0.96 - 1.08)
Current			
<20	0.66 (0.59 - 0.74)	0.64 (0.53 - 0.77)	0.82 (0.72 - 0.92)
≥ 20	0.49 (0.45 - 0.54)	0.47 (0.41 - 0.54)	0.65 (0.60 - 0.72)
Duration of smoking (yrs.)			
Never smoker	Ref	Ref	Ref
<5	1.06 (0.98 - 1.16)	1.1 (0.95 - 1.27)	1.07 (0.99 - 1.16)
5-9	1.11 (1.00 - 1.23)	1.08 (0.91 - 1.28)	1.01 (0.93 - 1.1)
10-19	1.05 (0.98 - 1.13)	1.22 (1.07 - 1.38)	1.01 (0.95 - 1.07)
20-29	0.99 (0.92 - 1.06)	1.04 (0.92 - 1.16)	1.01 (0.95 - 1.07)
30-39	0.87 (0.81 - 0.93)	0.86 (0.76 - 0.96)	0.95 (0.89 - 1.02)
40-49	0.69 (0.63 - 0.75)	0.67 (0.59 - 0.76)	0.86 (0.79 - 0.93)
≥50	0.65 (0.56 - 0.75)	0.68 (0.55 - 0.84)	0.73 (0.64 - 0.84)

*Multivariate-adjusted: Age, Ethnicity, BMI, Family history of cancer, Education level, Annual household income, Insurance, Health care provider, Marital status, Alcohol Intake

Table 1 shows the odds of a patient receiving a mammogram, Pap smear, or FOBT/endoscopy based on smoking status and relative to a never smoker. Current smoker status was associated with a significantly lower odd in cancer screening with mammography (OR 0.55; 95%CI: 0.51-0.59), Pap smear (OR 0.53; 95% CI: 0.47-0.59), and FOBT/endoscopy (OR 0.71; 95% CI: 0.66-0.76). In contrast, former smokers were significantly more likely than never smokers to receive mammogram (OR 1.05; 95% CI: 1.004-1.10) and Pap smear (OR 1.10; 95% CI: 1.02-1.18) but not FOBT/endoscopy (OR 1.03; 95% CI: 0.99-1.07).

A dose-dependent inverse trend between cigarettes per day and uptake of cancer screening was present among both current and former smokers. Lower odds in the receipt of mammograms is observed among former smokers who smoked ≥ 25 cigarettes per day (OR 0.94; 95% CI: 0.86-

1.01) compared to former smokers who smoked < 15 cigarettes per day (OR 1.1; 95% CI: 1.04-1.16). There is also a reduction in the receipt of Pap smears among current smokers with ≥ 25 cigarettes per day (OR 0.37; 95% CI: 0.29-0.48) compared to current smokers with < 15 cigarettes per day (OR 0.58; 95% CI: 0.5-0.68). This inverse relationship between smoking and cancer screening persists when patients are stratified by pack years. Within each stratum of smoking status ('former smoker' or 'current smoker'), patients with ≥ 20 pack year smoking history were less likely to receive cancer screening than their counterparts with < 20 pack year smoking history. Combining current and former smokers, there is a sharp decrease in cancer screenings among long-term smokers with ≥ 50 years of smoking history compared to never smokers: 35% lower odds of mammogram screening, 32% lower odds of Pap smear screening, and 27% lower odds of FOBT/endoscopy screening.

Table 2: OR and 95% CI of Late- vs. Early-Stage Breast & Colorectal Cancer Diagnoses by Smoking & Screening Status

		Breast Cancer		
Smoking Status	**Mammogram Ever**	**Mammogram Never OR (95% CI)***	**Mammogram ≤ 2 Years Ago**	**Mammogram > 2 Years Ago OR (95% CI)***
Overall	Ref	2.00 (1.35 - 2.94)	Ref	1.43 (1.18 - 1.75)
Never	Ref	1.59 (0.90 - 2.81)	Ref	1.32 (1.00 - 1.75)
Former	Ref	2.49 (1.33 - 4.67)	Ref	1.27 (1.00 - 1.89)
Current	Ref	2.95 (1.12 - 7.78)	Ref	2.78 (1.64 - 4.70)
		Colorectal Cancer		
Smoking Status	**FOBT/Endoscopy Ever**	**FOBT/Endoscopy Never OR (95% CI)†**	**FOBT/Endoscopy ≤ 5 Years Ago**	**FOBT/Endoscopy > 5 Years Ago OR (95% CI)†**
Overall	Ref	1.20 (0.90 - 1.61)	Ref	1.05 (0.79 - 1.39)

Never	Ref	1.12 (0.74 - 1.70)	Ref	0.96 (0.65 - 1.43)
Former	Ref	1.27 (0.82 - 1.96)	Ref	0.95 (0.62 - 1.48)
Current	Ref	1.19 (0.51 - 2.83)	Ref	2.25 (1.01 - 5.05)

*Multivariate-adjusted: Age, Ethnicity, BMI, Age at menarche, Age at first birth, Number of children breastfed, Hormone therapy use, Family history of breast cancer, History of benign breast disease, Education level, Annual household income, Insurance, Health care provider, Alcohol intake

†Multivariate-adjusted: Age, Ethnicity, BMI, Family history of colorectal cancer, Inflammatory bowel disease, Aspirin use, Education level, Annual household income, Insurance, Health care provider, Alcohol intake

For each stratum of smoking status, the odds ratio of being diagnosed with a late-stage cancer rather than an early-stage cancer is calculated for patients with no screening history or delinquent screening history ('Mammogram > 2 Years Ago' and 'FOBT/Endoscopy > 5 Years Ago') (Table 2). Overall, patients who never received mammograms (OR 2.00; 95% CI: 1.35 - 2.94) were twice as likely to be diagnosed with late-stage breast cancer compared to those who had received mammograms in the past. Diagnosis of late-stage breast cancer was significantly higher in current smokers who never had mammograms (OR 2.95; 95% CI: 1.12 - 7.78) or had their last mammogram > 2 years ago (OR 2.78; 95% CI: 1.64 - 4.70). There were no significant associations between history of cancer screening and cancer stage at diagnosis for patients who developed colorectal cancer. The one exception is current smokers who had FOBT/endoscopy performed > 5 years ago. These patients were more than twice as likely to present with late-stage colorectal cancer (OR 2.25; 95% CI: 1.01 - 5.05).

DISCUSSION

The U.S. Preventive Services Task Force (USPSTF) currently recommends biennial mammography screening for post-menopausal women up to the age of 74 years, and the American Cancer Society and American College of Physicians advise stool testing with sigmoidoscopy or colonoscopy every 5 to 10 years.[8–10] Numerous studies have demonstrated that smoking is associated with reduced utilization of preventive health services: fewer health examinations,[11] decreased vaccination rates,[12] and lower health insurance coverage.[13] Patterns of cancer screening among smokers and nonsmokers have also been variable and inconsistent. While some studies have found less compliance among smokers,[14–16] others were unable to find such association.[17–19]

Our study confirms that active smoking is inversely related to compliance with cancer screening recommendations, and that former smokers significantly surpass never smokers in seeking breast, cervical, and colorectal screening. Using responses from the 1990-1994 National Health Interview Surveys (NHIS), a study of women aged 42-75 similarly found adjusted odds of mammography and Pap test to be higher among former smokers and lower among current smokers who smoked > 1 pack per day.[20] A survey of 52,754 respondents aged ≥ 50 years also observed more FOBT or sigmoidoscopy among former smokers while current smoking status was inversely associated with colorectal cancer screening.[21] Although several studies have reported associations between smoking status and cancer screening, few have assessed this relationship in a dose-dependent manner. A national study of preventive services utilization had reported reduced receipt of breast, cervical, and colorectal cancer screening in daily smokers compared to non-daily smokers.[3] The current study further quantifies smoking severity in

additional dimensions and finds cancer screening to inversely correlate with frequency, amount, and duration of smoking.

Concern for personal health is the most common reason given for smoking cessation among former smokers and may explain why this health-conscious population seeks cancer screening more frequently than never smokers.[22] On the contrary, smokers are overly optimistic about their health and consistently underestimate the magnitude of their cancer risk.[23] This dichotomy in risk perception corresponds with our results indicating that current smokers have the lowest rates of screening while former smokers approach and, often, exceed never smokers in cancer screening, which could correspond to an overall advantage in seeking other preventive health behaviors.

Independent of smoking status, late-stage breast cancer rates were moderately elevated among all patients with inadequate screening. This study's results are in concordance with published associations between screening and late-stage presentation.[24,25] Mammograms aid in uncovering pre-cancerous lesions before their progression to malignant cancer.[26] As expected, our data demonstrates women who refuse regular mammography screening are likely to harbor later-stage breast cancer. These latent advanced cancers go undiagnosed if patients do not present to clinic for the opportunity to be screened. Of particular interest are current smokers who have the highest rate of developing a late-stage breast cancer if screening guidelines are not followed. The role of cigarette smoking in the etiology of breast cancer remains unclear – perhaps a higher risk of breast cancer could be due to less screening in addition to the genotoxic damage from smoke.[27,28] Nonetheless, active smokers fare the worst in cancer staging without recent testing.

Cancer screening is found to associate less with the detection of colorectal cancer as compared to breast cancer. However, this is not entirely surprising; 70-90% of colorectal cancers are first diagnosed clinically rather than via regularly scheduled FOBT/endoscopy screening. On the contrary, an estimated 90% of breast cancers are diagnosed with mammograms.[29,30] Thus, a significantly higher late vs. early presentation for colorectal cancer was only found among current smokers and underscores the importance of regular screening in this high-risk population. Furthermore, this WHI cohort had fewer incident cases of colorectal cancer compared with breast cancer (1,600 vs. 7,054 cases) thus reducing the statistical power for analyses with colorectal cancer.

The strengths of this study include the large study size, geographic diversity, and ethnic diversity of the WHI-OS participant cohort. The study also benefited from its prospective study design and regular annual adjudication of cancer events which, along with the exclusion of patients with pre-existing cancer diagnoses, mitigates concerns about reverse causation. The lengthy follow-up of 8.8 years allows us to associate lack of cancer screening with incidence of late stage cancers from the same participant cohort. Additional strengths include central adjudication of reported cancer cases and detailed information on known confounders and exposures that this study was able to take into account. Furthermore, this study assessed the dose-dependent association of smoking with cancer screening rates, which has not been done in many other studies.

Limitations of this study include the observational nature of this study and its focus on post-menopausal women. Baseline smoking status relied on self-report data and may be subject to recall bias. However, a meta-analysis has shown the validity and accuracy of self-reported

smoking to be high in most studies.[31] Lastly, we were not able to assess the association between smoking status and cervical cancer incidence due to the small number of incident cervical cancer cases in the WHI cohort.

CONCLUSION

In summary, active smoking is associated with decreased utilization of breast, colorectal, and cervical cancer screening services in a dose-dependent manner. Appropriate mammography screening is important for avoiding late-stage presentation in patients of all smoking statuses. Regular colorectal cancer screening also reduces the incidence of advanced colorectal cancer diagnoses among current smokers. Patients of all smoking histories should be encouraged to receive regular mammogram checks, especially active smokers who are less likely to seek screening. Although efficacy of colorectal cancer screening varies less by smoking status, public health initiatives should continue the effort of encouraging smoking cessation to minimize smoking-related morbidities.

AUTHORS' CONTRIBUTIONS

VAE, SPD, MSA, MLS, and JYP contributed to the study design and interpretation of data. VAE, SL, and JYP had full access to the data. SL performed the data extraction and analysis. VAE prepared the initial drafts of the manuscript with additional input from SPD, MLS, and JYP. VAE and MSA designed the tables with additional input from SPD, SL, MLS, and JYP. All authors contributed to the drafts and final version of the manuscript.

COMPETING INTERESTS

None declared

PATIENT CONSENT FOR PUBLICATION

Not required

DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the design of this study, the interpretation of the results, or preparation of the manuscript. However, patients are involved in the recruitment of additional participants to the Women's Health Initiative. Patients are also provided newsletters detailing the major findings from the database.

REFERENCES

1. Drope J, Schluger N, Cahn Z, et al. The Tobacco Atlas. *Am Cancer Soc Vital Strateg*. 2018.
2. Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study Collaborators. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet*. 2013;381(9861):133-141. doi:10.1016/S0140-6736(12)61720-6
3. Vander Weg MW, Howren MB, Cai X. Use of routine clinical preventive services among daily smokers, non-daily smokers, former smokers, and never-smokers. *Nicotine Tob Res*. 2012;14:123-130.
4. Kiefe CI, Williams OD, Greenlund KJ, CARDIA, J. Health care access and seven-year change in cigarette smoking. *Am Med*. 1998;15 SRC-G:146-154.
5. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9 Suppl):S107-21. doi:10.1016/S1047-2797(03)00047-4
6. Gail MH, Brinton LA, Byar DP, et al. Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who Are Being Examined Annually. *JNCI J Natl Cancer Inst*. 1989;81(24):1879-1886. doi:10.1093/jnci/81.24.1879
7. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*. 2010;116(3):544-573. doi:10.1002/cncr.24760
8. Siu AL. Screening for breast cancer: U.S. Preventive services task force recommendation statement. *Ann Intern Med*. 2016;164(4):279-296. doi:10.7326/M15-2886
9. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2006. *CA Cancer J Clin*. 2006;56(1):11-25. doi:10.3322/canjclin.56.1.11
10. Wilt TJ, Harris RP, Qaseem A, High Value Care Task Force of the American College of Physicians. Screening for cancer: advice for high-value care from the American College of Physicians. *Ann Intern Med*. 2015;162(10):718-725. doi:10.7326/M14-2326
11. Oakes T, Friedman G, Seltzer C, Siegelaub AB, Collen M. Health Service Utilization by Smokers and Nonsmokers. *Med Care*. 1974;12(11):858-966.
12. Stehr-Green PA, Sprauer MA, Williams WW, Sullivan KM. Predictors of vaccination behavior among persons ages 65 years and older. *Am J Public Health*. 1990;80(9):1127-1129. doi:10.2105/ajph.80.9.1127
13. Hurd MD, McGarry K. Medical insurance and the use of health care services by the elderly. *J Health Econ*. 1997;16(2):129-154. doi:10.1016/S0167-6296(96)00515-2
14. Fredman L, Sexton M, Cui Y, et al. Cigarette smoking, alcohol consumption, and screening mammography among women ages 50 and older. *Prev Med (Baltim)*. 1999;28(4):407-417. doi:10.1006/pmed.1998.0445
15. Lian M, Jeffe DB, Schootman M. Racial and Geographic Differences in Mammography Screening in St. Louis City: A Multilevel Study. *J Urban Heal*. 2008;85(5):677-692. doi:10.1007/s11524-008-9301-z
16. Carlos RC, Fendrick AM, Patterson SK, Bernstein SJ. Associations in breast and colon

cancer screening behavior in women. *Acad Radiol*. 2005;12(4):451-458. doi:10.1016/j.acra.2004.12.024

17. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and Smoking Cessation in Relation to Mortality in Women. *JAMA*. 2008;299(17):2037. doi:10.1001/jama.299.17.2037
18. Huncharek M, Haddock KS, Reid R, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*. 2010;100(4):693-701. doi:10.2105/AJPH.2008.150508
19. Eisen SA, Waterman B, Sugg Skinner C, et al. Sociodemographic and health status characteristics associated with prostate cancer screening in a national cohort of middle-aged male veterans. *Urology*. 1999;53(3):516-522. doi:10.1016/S0090-4295(98)00545-7
20. Rakowski W, Clark MA, Ehrich B. Smoking and Cancer Screening for Women Ages 42–75: Associations in the 1990–1994 National Health Interview Surveys. *Prev Med 48795*. 1999;29 SRC-:42-75.
21. Shapiro JA, Seeff LC, Nadel MR. Colorectal cancer-screening tests and associated health behaviors. *Am J Prev Med*. 2001;21(2):132-137. doi:10.1016/S0749-3797(01)00329-4
22. Hyland A, Li Q, Bauer JE, Giovino GA, Steger C, Cummings KM. Predictors of cessation in a cohort of current and former smokers followed over 13 years. *Nicotine Tob Res*. 2004;6(SUPPL. 3):363-369. doi:10.1080/14622200412331320761
23. Strecher VJ, Kreuter MW, Kobrin SC. Do cigarette smokers have unrealistic perceptions of their heart attack, cancer, and stroke risks? *J Behav Med*. 1995;18(1):45-54. doi:10.1007/BF01857704
24. Kronborg O1, Fenger C, Olsen J, Jørgensen OD SO. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996;Nov 30(348(9040)):1467-1471. doi:10.1016/S0140-6736(96)03430-7
25. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996;348(9040):1472-1477. doi:10.1016/S0140-6736(96)03386-7
26. Bleyer A, Welch HG. Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence. *N Engl J Med*. 2012;367(21):1998-2005. doi:10.1056/NEJMoa1206809
27. Terry PD, Rohan TE. Cigarette Smoking and the Risk of Breast Cancer in Women. *Cancer Epidemiol Biomarkers Prev*. 2002;8(9):733-739. http://cebp.aacrjournals.org/content/11/10/953.full-text.pdf. Accessed February 11, 2018.
28. Hecht SS. Tobacco smoke carcinogens and breast cancer. *Environ Mol Mutagen*. 2002;39(2-3):119-126. doi:10.1002/em.10071
29. Moreno CC, Mittal PK, Sullivan PS, et al. Colorectal Cancer Initial Diagnosis: Screening Colonoscopy, Diagnostic Colonoscopy, or Emergent Surgery, and Tumor Stage and Size at Initial Presentation. *Clin Colorectal Cancer*. 2016;15(1):67-73. doi:10.1016/j.clcc.2015.07.004
30. Smart CR, Hartmann WH, Beahrs OH, Garfinkel L. Insights into breast cancer screening of younger women. Evidence from the 14-year follow-up of the breast cancer detection demonstration project. *Cancer*. 1993;72(S4):1449-1456. doi:10.1002/1097-0142(19930815)72:4+<1449::AID-CNCR2820721406>3.0.CO;2-C
31. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health*. 1994;84(7):1086-1093. doi:10.2105/AJPH.84.7.1086

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The association between cigarette smoking, cancer screening, and cancer stage: A prospective study of the Women's Health Initiative Observational Cohort

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The association between cigarette smoking, cancer screening, and cancer stage: A prospective study of the Women's Health Initiative Observational Cohort

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KEYWORDS

Smoking Status

Cancer Screening

Cancer Stage

Breast Cancer

Cervical Cancer

Colorectal Cancer

ABSTRACT

Objective

To assess the dose-dependent relationship between smoking history and cancer screening rates or staging of cancer diagnoses.

Design

Prospective, population-based cohort study

Setting

Questionnaire responses from the Women's Health Initiative (WHI) Observational Study

Participants

89,058 postmenopausal women

Outcome Measures

Logistic regression models were used to assess the odds of obtaining breast, cervical, and colorectal cancer screening as stratified by smoking status. The odds of late-stage cancer diagnoses among patients with adequate versus inadequate screening as stratified by smoking status were also calculated.

Results

Of the 89,058 women who participated, 52.8% were never smokers, 40.8% were former smokers, and 6.37% were current smokers. Over an average of 8.8 years of follow-up, current smokers had lower odds of obtaining breast (OR 0.55; 95% CI: 0.51-0.59), cervical (OR 0.53; 95% CI: 0.47-0.59), and colorectal cancer (OR 0.71; 95% CI: 0.66-0.76) screening when compared to never smokers. Former smokers were more likely than never smokers to receive regular screening services. Failure to adhere to screening guidelines resulted in diagnoses at

higher cancer stages among current smokers for breast cancer (OR 2.78; 95% CI: 1.64-4.70) and colorectal cancer (OR 2.26; 95% CI: 1.01 - 5.05).

Conclusions

Active smoking is strongly associated with decreased utilization of cancer screening services and more advanced cancer stage at the time of diagnosis. Clinicians should emphasize the promotion of both smoking cessation and cancer screening for this high-risk group.

ARTICLE SUMMARY

Strengths and limitations of this study

- This study utilizes prospective data drawn from a national cohort of nearly 90,000 postmenopausal women with 8.8 years of follow-up and annual central adjudication of cancer cases.
- There is a possibility of recall bias and social desirability bias due to the use of self-reported questionnaire responses.
- There were not enough cases of cervical cancer in the cohort to analyze the relationship between smoking status and cervical cancer. Additionally, colorectal cancer screening was classified as receiving either FOBT or endoscopy within the past five years.

INTRODUCTION

Cigarette smoking is the single largest cause of cancer worldwide yet tobacco use is decreasing less rapidly in women than men, and lung cancer remains the leading cause of cancer death in women.[1,2] Data from mostly cross-sectional studies suggests that cancer screening services are underutilized in women, but other studies reported no association between smoking status and cancer screening; thus, additional research employing prospective follow-up could shed light on the relationship.[3] Because cigarette smoking is associated with other lifestyle risk factors, smoking status may also be associated with later stages of cancer presentation if healthcare is underutilized in this population.[4]

The Women's Health Initiative-Observational Cohort (WHI-OS) provides a unique opportunity to examine smoking as a barrier to cancer screening in a large, national cohort of multi-ethnic post-menopausal women. The present cross-sectional study will investigate use of cancer screening by smoking status, and determine whether the stage of cancer at the time of diagnosis varies based on smoking status among a nationally representative sample of women from the Women's Health Initiative-Observational Cohort (WHI-OS). We hypothesize that WHI-OS participants with history of smoking will have reduced use of cancer screening services and will have more advanced cancer stages at diagnosis. If smoking is associated with reduced cancer screening and more advanced cancer stages at diagnosis, then education and counseling interventions on the importance of cancer screening should be targeted to this high-risk group of individuals.

METHODS

Study Population - Women's Health Initiative

The Women's Health Initiative Observational Study recruited postmenopausal women from 40 clinical centers across the United States from October 1, 1993 to December 31, 1998. All WHI-OS participants had a physical examination at baseline and 3 years. Longitudinal data including demographics, risk exposures, health behaviors, and medical history were prospectively collected with annual mailed questionnaires. A central coordinating center established standardized data collection and reporting protocols for all study sites.[5] For this study, women with a diagnosis of cancer prior to or during the first year of the study were excluded from the analysis. Participants with unstaged cancers were also excluded. The design, eligibility criteria, and recruitment methods of WHI Observational Study (OS) have previously been described (National Clinical Trial identifier NCT00000611). Data provided to the authors for the purposes of this study were completely deidentified, and thus deemed exempt from review by the Stanford Institutional Review Board.

Definition of Exposures

Smoking status was defined from a self-reported questionnaire administered at study entry. Participants were classified as smokers if they answer 'Yes' to the question "During your entire life, have you smoked at least 100 cigarettes?" Smokers were further classified as current smokers or former smokers. Current and former smokers were then classified based on frequency, amount, and duration of smoking.

Definition of Cases

The primary outcome was cancer screening (yes vs. no) as determined by baseline self-reported receipt of mammogram, Papanicolaou/"Pap" test, fecal occult blood test (FOBT), sigmoidoscopy, and colonoscopy. Lung cancer screening using low-dose computed tomography was not yet available or recommended at the time of baseline assessments, so was not available for inclusion in our analyses.

The secondary outcome was cancer stage at diagnosis as determined by the Surveillance Epidemiology and End Results (SEER) 1988 classification method. Cancer outcomes were identified by an annual self-report questionnaire and centrally adjudicated by tumor registry coders. All *in situ* and localized cancers were classified as early stage cancers. Regional and distant cancers were classified as late stage cancers. Although breast, colorectal and cervical cancer are included in the screening analysis, only women diagnosed with incident breast and colorectal cancer were analyzed for cancer stage at presentation due to the small number of cervical cancer cases in the WHI-OS.

Statistical Analysis

Independent associations between smoking status and receipt of screening were investigated using separate multivariable logistic regression analyses with 95% confidence intervals (CIs) using never-smokers as the reference group within each table column. The following baseline covariates were accounted for in the statistical model: age, race/ethnicity, BMI, education, insurance type, usual care provider visit, and family history.

For cancer staging analysis, logistic regression models included all known cancer risk factors excluding smoking. Breast cancer covariates were based on the Gail model risk factors: sociodemographic characteristics, breast biopsy, family history of breast cancer, BMI, age at first birth, number of children breastfed, parity, and insurance type.[6] The colorectal model was adjusted for sociodemographic characteristics, insurance type, BMI, family history of colorectal cancer, aspirin use, and alcohol consumption.[7]

Smoking status ('Never', 'Former', 'Current') was the primary exposure of interest and all other analyses were considered of secondary interest. Secondary analyses were adjusted for multiple comparisons using the Bonferroni correction method. All tests were two-sided and tested at the 0.05 level of significance.

RESULTS

A total of 89,058 women were included in the analysis of which 47,021 were never-smokers, 36,360 were former smokers, and 5,677 were current smokers. From study enrollment in 1993 until data retrieval in 2017, patients were followed for a median of 8.8 years. Nearly all of never smokers (99.88%) remained never smokers, and former smokers (98.97%) remained former smokers. 49.49% of current smokers at baseline were no longer smoking by the last data collection. There were 7,054 incident cases of breast cancer, 1,600 incident cases of colorectal cancer, and 61 incident cases of cervical cancer.

Table 1: OR and 95% CIs of Reporting Breast, Cervical, and Colorectal Cancer Screening by Smoking Status

	Mammogram within the last 2 years OR (95% CI)*	**Pap smear within last 3 years OR (95% CI)***	**FOBT/Endoscopy within last 5 years OR (95% CI)***
Smoking status			
Never smoker	Ref	Ref	Ref
Current smoker	0.55 (0.51 - 0.59)	0.53 (0.47 - 0.59)	0.71 (0.66 - 0.76)
Former Smoker	1.05 (1.004 - 1.10)	1.10 (1.02 - 1.18)	1.03 (0.99 - 1.07)
Cigarettes per day			
Never smoker	Ref	Ref	Ref
Former			
<15	1.10 (1.04 - 1.16)	1.11 (1.01 - 1.21)	1.05 (0.998 - 1.10)
15-24	1.02 (0.95 - 1.10)	1.09 (0.97 - 1.22)	1.01 (0.95 - 1.07)
≥ 25	0.94 (0.86 - 1.01)	0.99 (0.87 - 1.13)	1.01 (0.94 - 1.08)
Current			
<15	0.63 (0.57 - 0.69)	0.58 (0.50 - 0.68)	0.78 (0.71 - 0.86)
15-24	0.47 (0.42 - 0.53)	0.53 (0.44 - 0.64)	0.63 (0.56 - 0.71)
≥ 25	0.49 (0.42 - 0.59)	0.37 (0.29 - 0.48)	0.65 (0.55 - 0.78)
Pack-years			

Never smoker	Ref	Ref	Ref
Former			
<20	1.11 (1.05 - 1.17)	1.13 (1.03 - 1.23)	1.04 (0.99 - 1.09)
≥ 20	0.96 (0.90 - 1.02)	0.99 (0.90 - 1.10)	1.02 (0.96 - 1.08)
Current			
<20	0.66 (0.59 - 0.74)	0.64 (0.53 - 0.77)	0.82 (0.72 - 0.92)
≥ 20	0.49 (0.45 - 0.54)	0.47 (0.41 - 0.54)	0.65 (0.60 - 0.72)
Duration of smoking (yrs.)			
Never smoker	Ref	Ref	Ref
<5	1.06 (0.98 - 1.16)	1.10 (0.95 - 1.27)	1.07 (0.99 - 1.16)
5-9	1.11 (1.00 - 1.23)	1.08 (0.91 - 1.28)	1.01 (0.93 - 1.10)
10-19	1.05 (0.98 - 1.13)	1.22 (1.07 - 1.38)	1.01 (0.95 - 1.07)
20-29	0.99 (0.92 - 1.06)	1.04 (0.92 - 1.16)	1.01 (0.95 - 1.07)
30-39	0.87 (0.81 - 0.93)	0.86 (0.76 - 0.96)	0.95 (0.89 - 1.02)
40-49	0.69 (0.63 - 0.75)	0.67 (0.59 - 0.76)	0.86 (0.79 - 0.93)
≥50	0.65 (0.56 - 0.75)	0.68 (0.55 - 0.84)	0.73 (0.64 - 0.84)

*Multivariate-adjusted: Age, Ethnicity, BMI, Family history of cancer, Education level, Annual household income, Insurance, Health care provider, Marital status, Alcohol Intake

Table 1 shows the odds of a patient receiving a mammogram, Pap smear, or FOBT/endoscopy based on smoking status and relative to a never smoker. Current smoker status was associated with a significantly lower odd in cancer screening with mammography (OR 0.55; 95%CI: 0.51-0.59), Pap smear (OR 0.53; 95% CI: 0.47-0.59), and FOBT/endoscopy (OR 0.71; 95% CI: 0.66-0.76). In contrast, former smokers were significantly more likely than never smokers to receive mammogram (OR 1.05; 95% CI: 1.004-1.10) and Pap smear (OR 1.10; 95% CI: 1.02-1.18) but not FOBT/endoscopy (OR 1.03; 95% CI: 0.99-1.07).

A dose-dependent inverse trend between cigarettes per day and uptake of cancer screening was present among both current and former smokers. Lower odds in the receipt of mammograms is observed among former smokers who smoked ≥ 25 cigarettes per day (OR 0.94; 95% CI: 0.86-

1.01) compared to former smokers who smoked < 15 cigarettes per day (OR 1.10; 95% CI: 1.04-1.16). There is also a reduction in the receipt of Pap smears among current smokers with ≥ 25 cigarettes per day (OR 0.37; 95% CI: 0.29-0.48) compared to current smokers with < 15 cigarettes per day (OR 0.58; 95% CI: 0.5-0.68). This inverse relationship between smoking and cancer screening persists when patients are stratified by pack years. Within each stratum of smoking status ('former smoker' or 'current smoker'), patients with ≥ 20 pack year smoking history were less likely to receive cancer screening than their counterparts with < 20 pack year smoking history. Combining current and former smokers, there is a sharp decrease in cancer screenings among long-term smokers with ≥ 50 years of smoking history compared to never smokers: 35% lower odds of mammogram screening, 32% lower odds of Pap smear screening, and 27% lower odds of FOBT/endoscopy screening.

Table 2: OR and 95% CI of Late- vs. Early-Stage Breast & Colorectal Cancer Diagnoses by Smoking & Screening Status

		Breast Cancer		
Smoking Status	**Mammogram Ever**	**Mammogram Never OR (95% CI)***	**Mammogram ≤ 2 Years Ago**	**Mammogram > 2 Years Ago OR (95% CI)***
Overall	Ref	2.00 (1.35 - 2.94)	Ref	1.43 (1.18 - 1.75)
Never	Ref	1.59 (0.90 - 2.81)	Ref	1.32 (1.00 - 1.75)
Former	Ref	2.49 (1.33 - 4.67)	Ref	1.27 (1.00 - 1.89)
Current	Ref	2.95 (1.12 - 7.78)	Ref	2.78 (1.64 - 4.70)
		Colorectal Cancer		
Smoking Status	**FOBT/Endoscopy Ever**	**FOBT/Endoscopy Never OR (95% CI)†**	**FOBT/Endoscopy ≤ 5 Years Ago**	**FOBT/Endoscopy > 5 Years Ago OR (95% CI)†**
Overall	Ref	1.20 (0.90 - 1.61)	Ref	1.05 (0.79 - 1.39)

Never	Ref	1.12 (0.74 - 1.70)	Ref	0.96 (0.65 - 1.43)
Former	Ref	1.27 (0.82 - 1.96)	Ref	0.95 (0.62 - 1.48)
Current	Ref	1.19 (0.51 - 2.83)	Ref	2.26 (1.01 - 5.05)

*Multivariate-adjusted: Age, Ethnicity, BMI, Age at menarche, Age at first birth, Number of children breastfed, Hormone therapy use, Family history of breast cancer, History of benign breast disease, Education level, Annual household income, Insurance, Health care provider, Alcohol intake

†Multivariate-adjusted: Age, Ethnicity, BMI, Family history of colorectal cancer, Inflammatory bowel disease, Aspirin use, Education level, Annual household income, Insurance, Health care provider, Alcohol intake

The odds ratio of being diagnosed with a late-stage cancer rather than an early-stage cancer was calculated for patients with no screening history or delinquent screening history ('Mammogram > 2 Years Ago' and 'FOBT/Endoscopy > 5 Years Ago') as stratified by smoking status (Table 2). Overall, patients who never received mammograms (OR 2.00; 95% CI: 1.35 - 2.94) were twice as likely to be diagnosed with late-stage breast cancer compared to those who had received mammograms in the past. More specifically, diagnosis of late-stage breast cancer was significantly higher in patients with a former history (OR 2.49; 95% CI: 1.33 – 4.67) or current history of smoking (OR 2.95; 95% CI: 1.12 - 7.78). Among patients who received their last mammogram > 2 years ago, current smokers were also significantly more likely to be diagnosed with a late-stage cancer (OR 2.78; 95% CI: 1.64 - 4.70). There were no significant associations between history of cancer screening and cancer stage at diagnosis for patients who developed colorectal cancer. The one exception is current smokers who had FOBT/endoscopy performed > 5 years ago. These patients were more than twice as likely to present with late-stage colorectal cancer (OR 2.26; 95% CI: 1.01 - 5.05).

DISCUSSION

The U.S. Preventive Services Task Force (USPSTF) currently recommends biennial mammography screening for post-menopausal women up to the age of 74 years, and the American Cancer Society and American College of Physicians advise stool testing with sigmoidoscopy or colonoscopy every 5 to 10 years.[8–10] Numerous studies have demonstrated that smoking is associated with reduced utilization of preventive health services: fewer health examinations,[11] decreased vaccination rates,[12] and lower health insurance coverage.[13] Patterns of cancer screening among smokers and nonsmokers have also been variable and inconsistent. While some studies have found less compliance among smokers,[14–16] others were unable to find such association.[17–19]

Our study confirms that active smoking is inversely related to compliance with cancer screening recommendations, and that former smokers significantly surpass never smokers in seeking breast, cervical, and colorectal screening. Using responses from the 1990-1994 National Health Interview Surveys (NHIS), a study of women aged 42-75 similarly found adjusted odds of mammography and Pap test to be higher among former smokers and lower among current smokers who smoked > 1 pack per day.[20] A survey of 52,754 respondents aged ≥ 50 years also observed more FOBT or sigmoidoscopy among former smokers while current smoking status was inversely associated with colorectal cancer screening.[21] Although several studies have reported associations between smoking status and cancer screening, few have assessed this relationship in a dose-dependent manner. A national study of preventive services utilization had reported reduced receipt of breast, cervical, and colorectal cancer screening in daily smokers compared to non-daily smokers.[3] The current study further quantifies smoking severity in

additional dimensions and finds cancer screening to inversely correlate with frequency, amount, and duration of smoking.

Concern for personal health is the most common reason given for smoking cessation among former smokers and may explain why this health-conscious population seeks cancer screening more frequently than never smokers.[22] On the contrary, smokers are overly optimistic about their health and consistently underestimate the magnitude of their cancer risk.[23] This dichotomy in risk perception corresponds with our results indicating that current smokers have the lowest rates of screening while former smokers approach and, often, exceed never smokers in cancer screening, which could correspond to an overall advantage in seeking other preventive health behaviors.

Independent of smoking status, late-stage breast cancer rates were moderately elevated among all patients with inadequate screening. This study's results are in concordance with published associations between screening and late-stage presentation.[24,25] Mammograms aid in uncovering early-stage breast cancer before they progress to more advanced cancer.[26] As expected, our data demonstrates women who refuse regular mammography screening are likely to harbor later-stage breast cancer. These latent advanced cancers go undiagnosed if patients do not present to clinic for the opportunity to be screened. Of particular interest are current smokers who have the highest rate of developing a late-stage breast cancer if screening guidelines are not followed. While the odds of late-stage breast cancer in never smokers did not vary significantly based on screening history (OR 1.59; 95% CI 0.90 - 2.81), active smokers with no history of mammography had a threefold increased odds of being diagnosed with a late-stage cancer (OR 2.95; 95% CI: 1.12 - 7.78). The role of cigarette smoking in the etiology of breast cancer remains

unclear – perhaps a higher risk of breast cancer could be due to less screening in addition to the genotoxic damage from smoke.[27,28] Nonetheless, active smokers without recent testing fare the worst in cancer staging and deserve targeted attention to ensure timely cancer screening.

Cancer screening is found to associate less with the detection of colorectal cancer as compared to breast cancer. However, unlike mammograms which detect cancerous lesions, FOBTs and endoscopies also detect precancerous adenomas in addition to cancerous polyps. Thus, a difference in the ratio of late-stage cancer versus early-stage or precancerous lesions may only become apparent among those with significant risk factors such as smoking. Thus, a significantly higher late vs. early presentation for colorectal cancer was only found among current smokers and underscores the importance of regular screening in this high-risk population. Furthermore, this WHI cohort had fewer incident cases of colorectal cancer compared with breast cancer (1,600 vs. 7,054 cases) thus reducing the statistical power for analyses with colorectal cancer.

The strengths of this study include the large study size, geographic diversity, and ethnic diversity of the WHI-OS participant cohort. The study also benefited from its prospective study design and regular annual adjudication of cancer events which, along with the exclusion of patients with pre-existing cancer diagnoses, mitigates concerns about reverse causation. The lengthy follow-up of 8.8 years allows us to associate lack of cancer screening with incidence of late stage cancers from the same participant cohort. Additional strengths include central adjudication of reported cancer cases and detailed information on known confounders and exposures that this study was able to take into account. Furthermore, this study assessed the dose-dependent association of smoking with cancer screening rates, which has not been done in many other studies.

Limitations of this study include the observational nature of this study and its focus on post-menopausal women. Self-reported data on smoking and cancer screening may be subject to recall bias and social desirability bias. Although the validity and accuracy of self-reported smoking to be high in most studies, overreporting of preventive health behaviors remains common and difficult to quantify.[29,30] Current guidelines for colorectal cancer screening recommend annual FOBT and endoscopy every five years. However, colorectal cancer screening was recorded in the study dataset by having had either a FOBT or an endoscopy within the past five years. Thus, we were unable to provide a separate analysis with shorter time intervals using annual FOBT results. Lastly, we were not able to assess the association between smoking status and cervical cancer incidence due to the small number of incident cervical cancer cases in the WHI cohort.

CONCLUSION

In summary, active smoking is associated with decreased utilization of breast, colorectal, and cervical cancer screening services in a dose-dependent manner. Additionally, while cancer screening is important for avoiding late-stage presentation in patients of all smoking statuses, active smokers without appropriate screening have significantly higher odds of being diagnosed with an advanced breast or colorectal cancer. Patients of all smoking histories should be encouraged to receive regular mammogram and FOBT/endoscopy, particularly active smokers who are less likely to seek screening. Public health initiatives should continue the effort of encouraging smoking cessation to minimize smoking-related morbidities.

AUTHORS' CONTRIBUTIONS

VAE, SPD, MSA, MLS, and JYP contributed to the study design and interpretation of data. VAE, SL, and JYP had full access to the data. SL performed the data extraction and analysis. VAE prepared the initial drafts of the manuscript with additional input from SPD, MLS, and JYP. VAE and MSA designed the tables with additional input from SPD, SL, MLS, and JYP. All authors contributed to the drafts and final version of the manuscript.

COMPETING INTERESTS

None declared

PATIENT CONSENT FOR PUBLICATION

Not required

DATA AVAILABILITY STATEMENT

Data used in this study is hosted by the Women's Health Initiative and was fully deidentified and anonymized prior to receipt by the study authors. Eligible researchers may download the study protocol, study procedures, data collection forms, and deidentified participant data directly at the WHI online resource (https://www.whi.org/researchers/data/Pages/Home.aspx). Other researchers may download the publicly available data through BioLINCC (https://biolincc.nhlbi.nih.gov/studies/whict).

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the design of this study, the interpretation of the results, or preparation of the manuscript. However, patients are involved in the recruitment of additional participants to the Women's Health Initiative. Patients are also provided newsletters detailing the major findings from the database.

REFERENCES

1. Drope J, Schluger N, Cahn Z, et al. The Tobacco Atlas. *Am Cancer Soc Vital Strateg*. 2018.
2. Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study Collaborators. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet*. 2013;381(9861):133-141. doi:10.1016/S0140-6736(12)61720-6
3. Vander Weg MW, Howren MB, Cai X. Use of routine clinical preventive services among daily smokers, non-daily smokers, former smokers, and never-smokers. *Nicotine Tob Res*. 2012;14:123-130.
4. Kiefe CI, Williams OD, Greenlund KJ, CARDIA, J. Health care access and seven-year change in cigarette smoking. *Am Med*. 1998;15 SRC-G:146-154.
5. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9 Suppl):S107-21. doi:10.1016/S1047-2797(03)00047-4
6. Gail MH, Brinton LA, Byar DP, et al. Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who Are Being Examined Annually. *JNCI J Natl Cancer Inst*. 1989;81(24):1879-1886. doi:10.1093/jnci/81.24.1879
7. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*. 2010;116(3):544-573. doi:10.1002/cncr.24760
8. Siu AL. Screening for breast cancer: U.S. Preventive services task force recommendation statement. *Ann Intern Med*. 2016;164(4):279-296. doi:10.7326/M15-2886
9. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society Guidelines for the Early Detection of Cancer, 2006. *CA Cancer J Clin*. 2006;56(1):11-25. doi:10.3322/canjclin.56.1.11
10. Wilt TJ, Harris RP, Qaseem A, High Value Care Task Force of the American College of Physicians. Screening for cancer: advice for high-value care from the American College of Physicians. *Ann Intern Med*. 2015;162(10):718-725. doi:10.7326/M14-2326
11. Oakes T, Friedman G, Seltzer C, Siegelaub AB, Collen M. Health Service Utilization by Smokers and Nonsmokers. *Med Care*. 1974;12(11):858-966.
12. Stehr-Green PA, Sprauer MA, Williams WW, Sullivan KM. Predictors of vaccination behavior among persons ages 65 years and older. *Am J Public Health*. 1990;80(9):1127-1129. doi:10.2105/ajph.80.9.1127
13. Hurd MD, McGarry K. Medical insurance and the use of health care services by the elderly. *J Health Econ*. 1997;16(2):129-154. doi:10.1016/S0167-6296(96)00515-2
14. Fredman L, Sexton M, Cui Y, et al. Cigarette smoking, alcohol consumption, and screening mammography among women ages 50 and older. *Prev Med (Baltim)*. 1999;28(4):407-417. doi:10.1006/pmed.1998.0445
15. Lian M, Jeffe DB, Schootman M. Racial and Geographic Differences in Mammography Screening in St. Louis City: A Multilevel Study. *J Urban Heal*. 2008;85(5):677-692. doi:10.1007/s11524-008-9301-z
16. Carlos RC, Fendrick AM, Patterson SK, Bernstein SJ. Associations in breast and colon

cancer screening behavior in women. *Acad Radiol*. 2005;12(4):451-458. doi:10.1016/j.acra.2004.12.024

17. Kenfield SA, Stampfer MJ, Rosner BA, Colditz GA. Smoking and Smoking Cessation in Relation to Mortality in Women. *JAMA*. 2008;299(17):2037. doi:10.1001/jama.299.17.2037
18. Huncharek M, Haddock KS, Reid R, Kupelnick B. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*. 2010;100(4):693-701. doi:10.2105/AJPH.2008.150508
19. Eisen SA, Waterman B, Sugg Skinner C, et al. Sociodemographic and health status characteristics associated with prostate cancer screening in a national cohort of middle-aged male veterans. *Urology*. 1999;53(3):516-522. doi:10.1016/S0090-4295(98)00545-7
20. Rakowski W, Clark MA, Ehrich B. Smoking and Cancer Screening for Women Ages 42–75: Associations in the 1990–1994 National Health Interview Surveys. *Prev Med 48795*. 1999;29 SRC-:42-75.
21. Shapiro JA, Seeff LC, Nadel MR. Colorectal cancer-screening tests and associated health behaviors. *Am J Prev Med*. 2001;21(2):132-137. doi:10.1016/S0749-3797(01)00329-4
22. Hyland A, Li Q, Bauer JE, Giovino GA, Steger C, Cummings KM. Predictors of cessation in a cohort of current and former smokers followed over 13 years. *Nicotine Tob Res*. 2004;6(SUPPL. 3):363-369. doi:10.1080/14622200412331320761
23. Strecher VJ, Kreuter MW, Kobrin SC. Do cigarette smokers have unrealistic perceptions of their heart attack, cancer, and stroke risks? *J Behav Med*. 1995;18(1):45-54. doi:10.1007/BF01857704
24. Kronborg O1, Fenger C, Olsen J, Jørgensen OD SO. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996;Nov 30(348(9040)):1467-1471. doi:10.1016/S0140-6736(96)03430-7
25. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996;348(9040):1472-1477. doi:10.1016/S0140-6736(96)03386-7
26. Bleyer A, Welch HG. Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence. *N Engl J Med*. 2012;367(21):1998-2005. doi:10.1056/NEJMoa1206809
27. Terry PD, Rohan TE. Cigarette Smoking and the Risk of Breast Cancer in Women. *Cancer Epidemiol Biomarkers Prev*. 2002;8(9):733-739. http://cebp.aacrjournals.org/content/11/10/953.full-text.pdf. Accessed February 11, 2018.
28. Hecht SS. Tobacco smoke carcinogens and breast cancer. *Environ Mol Mutagen*. 2002;39(2-3):119-126. doi:10.1002/em.10071
29. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. *Am J Public Health*. 1994;84(7):1086-1093. doi:10.2105/AJPH.84.7.1086
30. Newell SA, Girgis A, Sanson-Fisher RW, Savolainen NJ. The accuracy of self-reported health behaviors and risk factors relating to cancer and cardiovascular disease in the general population: A critical review. *Am J Prev Med*. 1999;17(3):211-229. doi:10.1016/S0749-3797(99)00069-0

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.