Research Article

Cancer Epidemiology, Biomarkers & Prevention

# Cigarette Smoking, Physical Activity, and Alcohol Consumption as Predictors of Cancer Incidence among Women at High Risk of Breast Cancer in the NSABP P-1 Trial

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## Abstract

**Background:** NSABP P-1 provides an opportunity to examine the association of behavioral factors with prospectively monitored cancer incidence and interactions with tamoxifen.

**Methods:** From 1992 to 1997, 13,388 women with estimated 5-year breast cancer risk greater than 1.66% or a history of lobular carcinoma *in situ* (87% younger than age 65; 67% postmenopausal) were randomly assigned to tamoxifen versus placebo. Invasive breast cancer, lung cancer, colon cancer, and endometrial cancer were analyzed with Cox regression. Predictors were baseline cigarette smoking, leisure-time physical activity, alcohol consumption, and established risk factors.

**Results:** At median 7 years follow-up, we observed 395, 66, 35, and 74 breast cancer, lung cancer, colon cancer, and endometrial cancer, respectively. Women who had smoked were at increased risk of breast cancer ($P = 0.007$; HR = 1.3 for 15–35 years smoking, HR = 1.6 for ≥35 years), lung cancer ($P < 0.001$; HR = 3.9 for 15–35 years, HR = 18.4 for ≥35 years), and colon cancer ($P < 0.001$; HR = 5.1 for ≥35 years) versus never-smokers. Low activity predicted increased breast cancer risk only among women assigned to placebo ($P = 0.021$ activity main effect, $P = 0.013$ activity–treatment interaction; HR = 1.4 for the placebo group) and endometrial cancer among all women ($P = 0.026$, HR = 1.7). Moderate alcohol (>0–1 drink/day) was associated with decreased risk of colon cancer ($P = 0.019$; HR = 0.35) versus no alcohol. There were no other significant associations between these behaviors and cancer risk.

**Conclusion:** Among women with elevated risk of breast cancer, smoking has an even greater impact on breast cancer risk than observed in past studies in the general population.

**Impact:** Women who smoke or are inactive should be informed of the increased risk of multiple types of cancer. *Cancer Epidemiol Biomarkers Prev; 23(5); 823–32. ©2014 AACR.*

## Introduction

Cigarette smoking, physical activity, and alcohol consumption have been implicated in previous studies as risk or protective factors for cancer at a number of organ sites. Cigarette smoking, long known to increase the risk of lung cancer, is also associated with increased risk of many other cancers, including those of the colon and breast (1–10). There is an inverse effect of cigarette smoking for endometrial cancer, especially among postmenopausal overweight or obese women (due possibly to an antiestrogenic effect of smoking; refs. 11–16). Physical activity seems to be a protective factor for many cancers (17–21). Alcohol consumption has been associated with increased risks of breast, lung, and colon cancer, among others (22–24). The evidence is stronger for some of these associations than others, and the generalizability across populations varies as well.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT, also known as P-1) tested the drug tamoxifen for the reduction of the rate of breast cancer in high-risk women without a history of breast cancer. NSABP P-1 results indicated that a 5-year course of daily tamoxifen was associated with a 50% reduction in the primary incidence of invasive breast cancer relative to a placebo (25). In NSABP P-1, participants reported their baseline cigarette smoking history, leisure-time physical activity, and alcohol consumption. NSABP P-1 provides an important opportunity to examine the association of behavioral risk factors with prospectively monitored cancer incidence in a

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cohort of women at high risk of breast cancer. In this primary report of behavioral risk factors and cancer incidence in NSABP P-1, we examine the associations of baseline cigarette smoking history, leisure-time physical activity, and alcohol consumption, with the 4 most commonly occurring cancers among NSABP P-1 participants: invasive cancer of the breast, lung, colon, and endometrium.

## Materials and Methods

### Participants

This is a secondary analysis of the NSABP P-1 database. NSABP P-1, which was funded by the National Cancer Institute, was a double-blinded, placebo-controlled clinical trial that was open for accrual at several hundred clinical centers throughout North America from June 1, 1992, through September 30, 1997. During this interval, 13,388 women were randomly assigned to receive either 20 mg/day of tamoxifen or placebo for a duration of 5 years (25). The risk of breast cancer was estimated using the Gail model, which incorporates a woman's age at menarche, number of benign breast biopsies, histologic diagnosis of atypical hyperplasia, nulliparity or age at first live birth, and number of first-degree relatives with breast cancer (26). Participants were required to have an estimated 5-year risk greater than 1.66% or a history of lobular carcinoma *in situ* (LCIS). They must have discontinued hormone use (hormone replacement or oral contraceptives) 3 months before enrollment. Exclusion criteria included a history of cancer (other than basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix) within the prior 10 years, or any history of breast cancer other than LCIS. All participants provided informed consent, which was approved by the Institutional Review Boards of all participating institutions.

### Cancer surveillance

Participants underwent clinical examinations (including medical history since last visit, height, weight, physical breast exam, complete blood count, platelet count, alkaline phosphatase, calcium, liver functions, and renal tests) every 6 months, and gynecologic examinations and mammograms annually. Documentation of all cancer events and all hospitalizations was reviewed centrally to verify cancer diagnoses. After a first diagnosis of cancer, surveillance continued, so that the first invasive event at each organ site was reported independently.

### Measures

A patient-reported instrument administered upon enrollment collected cigarette smoking data (at least 100 cigarettes in lifetime, age of initiation, current smoking frequency and intensity, past intensity, and age at quitting if a former smoker). The instrument also provided descriptions of physical inactivity, and light, moderate, or vigorous physical activity. Participants were asked to select one of these 4 levels to describe their activity during their leisure time in the previous 12 months. Frequency and quantity (serving size and number of servings consumed) of beer, wine, and liquor over the previous 12 months were reported in separate items. Items were adapted from the Postmenopausal Estrogen/Progestin Interventions Trial (27).

### Statistical considerations

Separate multivariable Cox proportional hazards regression analyses were conducted for the time from random assignment to the diagnosis of invasive cancer of the breast, lung, colon, and endometrium. Time was censored at the date of last follow-up or date of death without evidence of the particular cancer. We provide results for smoking duration, classified as never, <15 years, 15 to 35 years, and ≥35 years [using cutoffs of 15 and 35 years based on an example colon cancer prediction tool (28) and the PDQ Smoking in Cancer Care evidence review published by the National Cancer Institute that found increased colorectal cancer risk after 35 years of smoking]. Because there is not a consensus about the best measures of cigarette smoking history (29), we provide results for candidate alternative measures in the Supplementary Appendix: smoking status at baseline (current, former, never); intensity (none, 0–1 pack per day, or >1 pack per day); and additional candidate variables derived from duration, status, and intensity. Physical activity was classified *a priori* as inactive/light versus moderate/heavy. The quantities of alcoholic beverages were first converted to a common unit "drink" [12 oz. (355 mL) beer, 5 oz. (148 mL) wine, or 1.5 oz. (44 ml) spirits] and then added across beer, wine, and liquor. Alcohol consumption was classified *a priori* as none, 1, or more than 1 drink/day, on average, distinguishing healthy or unhealthy consumption based on the 2005 U.S. Department of Agriculture recommendation that women who choose to drink limit their consumption to up to 1 drink/day on average, following the approach used in a recent publication (30). We fit one model for each cancer disease site, including smoking duration, physical activity, alcohol consumption, and other candidate predictors that were selected *a priori* based on existing literature on risk factors and primary cancer incidence. The variables included in each disease site model are indicated in Table 1 (characteristics column). Assigned treatment group, age (≥65 years), participant-reported race/ethnicity, menopausal status, and prior estrogen use were included as candidate predictors of risk for the analysis of all of the organ sites of cancer being assessed. Other candidate predictors included for analyses differed by cancer site being assessed. Estimated breast cancer risk (Gail score analyzed as a continuous variable) and diabetes were also included for the analysis of breast cancer incidence. Family cancer history and personal history of tuberculosis were included for the analysis of lung cancer. For the analysis of colon cancer, family cancer history and current

**Table 1.** Participant characteristics: NSABP P-1

| Characteristic[a] | Placebo *N* = 6,707 (50.1%) *N* (%) | Tamoxifen *N* = 6,681 (49.9%) *N* (%) | Total (*N* = 13,388) *N* (%) |
|---|---|---|---|
| Age, y (B, L, C, E) | | | |
| <65 | 5797 (86.4) | 5783 (86.6) | 11,580 (86.5) |
| ≥65 | 910 (13.6) | 898 (13.4) | 1,808 (13.5) |
| Race (B, L, C, E) | | | |
| White | 6,352 (94.7) | 6,337 (94.8) | 12,689 (94.8) |
| Black | 133 (2) | 143 (2.1) | 276 (2.1) |
| Hispanic | 94 (1.4) | 73 (1.1) | 167 (1.2) |
| Other/unknown | 128 (1.9) | 128 (2) | 256 (1.9) |
| Leisure-time physical activity (B, L, C, E) | | | |
| Moderate–heavy | 3,058 (45.6) | 3,067 (45.9) | 6,125 (45.7) |
| Inactive–light | 3,626 (54.1) | 3,586 (53.7) | 7,212 (53.9) |
| Unknown | 23 (0.3) | 28 (0.4) | 51 (0.4) |
| Baseline BMI (B[b], E[b]) | | | |
| Healthy (BMI < 25) | 2,603 (38.8) | 2,635 (39.4) | 5,238 (39.1) |
| Overweight (BMI ≥25 to <30) | 2,233 (33.3) | 2,157 (32.3) | 4,390 (32.8) |
| Obese (BMI ≥ 30) | 1,871 (27.9) | 1,889 (28.3) | 3,760 (28.1) |
| Alcohol consumption (B, L, C, E) | | | |
| None | 1,421 (21.2) | 1,366 (20.5) | 2,787 (20.8) |
| 1 drink/day | 4,383 (65.3) | 4,439 (66.4) | 8,822 (65.9) |
| >1 drink/day | 877 (13.1) | 847 (12.7) | 1,724 (12.9) |
| Unknown | 26 (0.4) | 29 (0.4) | 55 (0.4) |
| Smoking status (B, L, C, E) | | | |
| Never smoked | 3,707 (55.3) | 3,612 (54.1) | 7,319 (54.7) |
| Current smoker | 827 (12.3) | 847 (12.7) | 1,674 (12.5) |
| Former smoker | 2,150 (32.1) | 2,195 (32.8) | 4,345 (32.5) |
| Unknown | 23 (0.3) | 27 (0.4) | 50 (0.4) |
| Smoking duration (B, L, C, E) | | | |
| Never smoked[c] | 3,715 (55.4) | 3,620 (54.2) | 7,335 (54.8) |
| <15 smoking years | 839 (12.5) | 825 (12.3) | 1,664 (12.4) |
| ≥15 to <35 smoking years | 1,607 (24) | 1,707 (25.6) | 3,314 (24.8) |
| ≥35 smoking years | 514 (7.7) | 497 (7.4) | 1,011 (7.6) |
| Unknown | 32 (0.5) | 32 (0.5) | 64 (0.5) |
| Smoking intensity (B, L, C, E) | | | |
| None | 3,707 (55.3) | 3,612 (54.1) | 7,319 (54.7) |
| 1 pack/day | 2,008 (29.9) | 2,069 (31) | 4,077 (30.5) |
| >1 packs/day | 968 (14.4) | 972 (14.5) | 1,940 (14.5) |
| Unknown | 24 (0.4) | 28 (0.4) | 52 (0.4) |
| 5-Year breast cancer risk (B[d]) | | | |
| ≤2% | 1,682 (25.1) | 1,677 (25.1) | 3,359 (25.1) |
| >2% and ≤5% | 3,895 (58.1) | 3,823 (57.2) | 7,718 (57.6) |
| >5% | 1,130 (16.8) | 1,181 (17.7) | 2,311 (17.3) |
| Family cancer history (number of family members who developed cancer; L, C, E) | | | |
| None | 759 (11.3) | 731 (10.9) | 1,490 (11.1) |
| 1 | 2,709 (40.4) | 2,717 (40.7) | 5,426 (40.5) |
| >1 | 3,183 (47.5) | 3,182 (47.6) | 6,365 (47.5) |
| Unknown | 56 (0.8) | 51 (0.8) | 107 (0.8) |
| Menstrual period stopped (B, L, C, E) | | | |
| No | 2,254 (33.6) | 2,159 (32.8) | 4,449 (33.2) |
| Yes | 4,453 (66.4) | 4,486 (67.2) | 8,939 (66.8) |

*(Continued on the following page)*

**Table 1.** Participant characteristics: NSABP P-1 (Cont'd)

| Characteristic[a] | Placebo $N = 6{,}707$ (50.1%) *N* (%) | Tamoxifen $N = 6{,}681$ (49.9%) *N* (%) | Total ($N = 13{,}388$) *N* (%) |
|---|---|---|---|
| Estrogen use (B, L, C, E) | | | |
| Never used | 1,619 (24.1) | 1,542 (23.1) | 3,161 (23.6) |
| Ever used | 5,088 (75.9) | 5,139 (76.9) | 10,227 (76.4) |
| Age at menarche (years; E) | | | |
| 7–10 | 567 (8.5) | 576 (8.6) | 1,143 (8.5) |
| 11–13 | 4,868 (72.6) | 4,902 (73.4) | 9,770 (73) |
| ≥14 | 1,243 (18.5) | 1,180 (17.7) | 2,423 (18.1) |
| Unknown | 29 (0.4) | 23 (0.3) | 52 (0.4) |
| Ever had diabetes (B, E) | | | |
| No | 6,443 (96.1) | 6,402 (95.8) | 12,845 (95.9) |
| Yes | 264 (3.9) | 279 (4.2) | 543 (4.1) |
| Past pregnancy (E) | | | |
| No | 1,011 (15.1) | 1,009 (15.1) | 2,020 (15.1) |
| Yes | 5,690 (84.8) | 5,669 (84.9) | 11,359 (84.8) |
| Unknown | 6 (0.1) | 3 (0) | 9 (0.1) |
| Current regular aspirin use (C) | | | |
| No | 5,651 (84.3) | 5,610 (84.0) | 11,261 (84.1) |
| Yes | 1,056 (15.7) | 1,071 (16.0) | 2,127 (15.9) |
| Personal history of tuberculosis (L) | | | |
| No | 6,629 (98.8) | 6,581 (98.5) | 13,210 (98.7) |
| Yes | 78 (1.2) | 100 (1.5) | 178 (1.3) |

[a]Characteristic included in disease site models in parentheses: breast (B), lung (L), colon (C), and endometrial (E).

[b]Overweight/obesity was included in secondary analyses for models with significant effects of physical activity. These were the models for breast and endometrial cancers.

[c]Includes former smokers who indicated 0 years of smoking history.

[d]Estimated breast cancer risk is included as a continuous variable in models.

aspirin use were included. Age at menarche, number of past pregnancies, family cancer history, and diabetes were included for the analysis of endometrial cancer. Pretreatment values were used for all explanatory variables. Stepwise selection determined the medical/demographic factors to include in the final model for each organ site. Candidate interactions tested were: 2- and 3-way interactions between treatment group, smoking, and menstrual status. In the model for breast cancer, we also tested whether the effect of tamoxifen on breast cancer incidence was modified by alcohol consumption or physical activity at the time of random assignment. The significance of explanatory variables was tested at 2-sided $\alpha$ level 0.05.

Height and weight were also measured at each follow-up, from which we computed body mass index (BMI). However, BMI is not a focus of the present report, as it has been examined in detail as a predictor of breast cancer separately (31). Overweight/obesity has also been identified in previous literature as a risk factor for endometrial cancers. However, it may be on the same causal pathway as physical activity, and we were interested in physical activity as a factor in cancer prevention, whether or not it acts through obesity reduction. Therefore, our primary analyses did not adjust for overweight/obesity. [For further discussion of this issue, see Moore and colleagues (32)]. Secondary analyses were performed to examine whether findings for physical activity were independent of being overweight/obese. In the model for endometrial cancer that accounted for being overweight/obese, we tested 2 and 3-way interactions between being overweight/obese, menopausal status, and smoking duration.

Computations were performed in SAS 9.2.

## Results

Of 13,388 enrolled participants, clinical follow-up was available for 13,208 (98.7%). Forty-seven participants (<1%) withdrew from study before starting therapy; 95 (<1%) withdrew from study after starting therapy; and 38 (<1%) were without follow-up for other reasons. The present report is based on a cut-off of 7 years of follow-up, in keeping with the most recent update of breast cancer incidence (33). Participants' mean age was 54; 8,939 (67%) were postmenopausal (see Table 1). During follow-up, invasive cancers of the breast, lung, colon, and endometrium were reported for 395, 66, 35, and 74 women, respectively. Very few women had more than one cancer of these sites: 1 had both colon and breast and 3 had endometrial and breast cancers.

## Cigarette smoking

There were 7,335 participants (54.8%) who had never smoked cigarettes or reported smoking 0 years; 1,664 (12.4%) former or current smokers who smoked >0 to 15 years; 3,314 (24.8%) who smoked 15 to 35 years; and 1,011 (7.6%) who smoked at least 35 years. Smoking duration was unknown for 64 women. In the multivariable model (accounting for treatment, alcohol consumption, leisure time physical activity, and major risk factors), smoking duration was associated with an increased risk of breast cancer ($P = 0.007$; multivariable HR = 1.34; 95% confidence interval (CI), 1.06–1.69 for women who had smoked 15 to 35 years and HR = 1.58; 95% CI, 1.11–2.26 for women who smoked at least 35 years, both as compared with never smokers; see Supplementary Appendix Table A1 and Figs. 1 and 2). Smoking duration was also associated with an increased risk of lung cancer ($P < 0.001$; HR = 3.89; 95% CI, 1.88–8.06 for women who smoked 15 to 35 years and HR = 18.45; 95% CI, 9.35–36.41 for women who smoked for ≥35 years, as compared with never smokers; see Appendix Table A1 and Fig. 2). The multivariable association of cigarette smoking with colon cancer was significant ($P < 0.001$), but was evident only for women who smoked ≥35 years (HR = 5.11; 95% CI, 2.30–11.37; see Appendix Table A1 and Fig. 1B). Smoking duration was not significantly associated with the risk of endometrial cancer ($P = 0.25$; see Appendix Table A1 and Fig. 2). There was no significant 2- or 3-way interaction between tamoxifen assignment, smoking duration, and menstrual status in the full multivariable analyses of breast, colon, lung, or endometrial cancers. The interaction between treatment assignment and smoking status in the analysis of breast cancer was also nonsignificant ($P = 0.56$, see Supplementary Appendix). In the secondary analysis for endometrial cancer that accounted for overweight/obesity, there were no significant 2- or 3-way interactions between overweight/obesity, menopausal status, and smoking duration (data not shown). Analyses with alternative measures of smoking status and history are provided in the Supplementary Appendix. Of note, smoking status at baseline did not significantly predict breast cancer risk ($P = 0.074$).

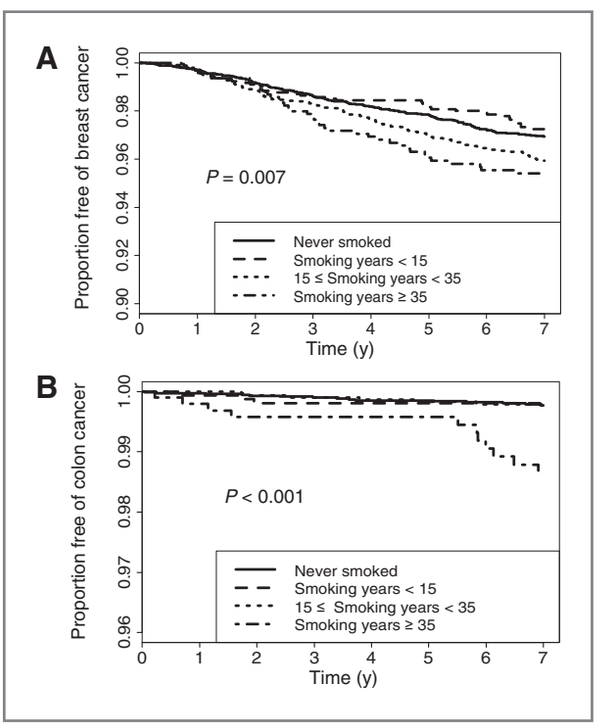


Figure 1. Kaplan–Meier graph of the time to breast cancer event (A) or colon cancer (B), grouped according to smoking duration. *P* values are based on multivariable Cox regression analysis.

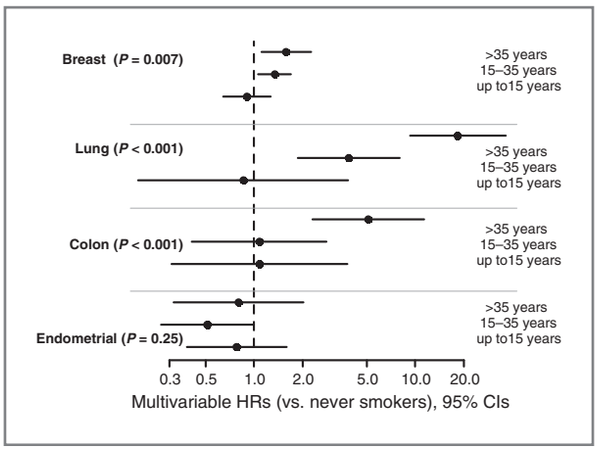


Figure 2. HRs and 95% CIs for the association of cigarette smoking history with time to invasive cancer of the breast, lung, colon, and endometrium.

## Leisure-time physical activity

A total of 7,212 women (53.9%) reported that they typically engaged in low levels of leisure-time physical activity or were inactive. In the multivariable model that accounted for treatment, alcohol consumption, smoking duration, and major risk factors, less active women were at significantly greater risk of breast cancer (main effect $P = 0.021$), and there was a significant interaction between physical activity and treatment ($P = 0.013$). Specifically, low/no activity was associated with a physical activity (PA) hazard ratio $HR_{PA} = 1.35$ and 95% CI, 1.05–1.75 for women assigned to placebo, as compared with more active women; but for women assigned to tamoxifen, $HR_{PA}$ was nonsignificant ($HR_{PA} = 0.80$; 95% CI, 0.58–1.11). The effect of tamoxifen on breast cancer risk was stronger in less active women ($HR_{TAM} = 0.45$; 95% CI, 0.34–0.59) than in more active women ($HR_{TAM} = 0.75$; 95% CI, 0.56–1.02). The risks of lung and colon cancers were not associated with activity ($P = 0.4$, HR = 0.8; $P = 0.8$, HR = 0.9, for lung and colon, respectively). Women with low/no physical activity were at a 70% greater risk of endometrial cancer ($P = 0.026$; HR = 1.73; 95% CI, 1.07–2.80; see Fig. 3). Significant findings were retested in secondary analyses that

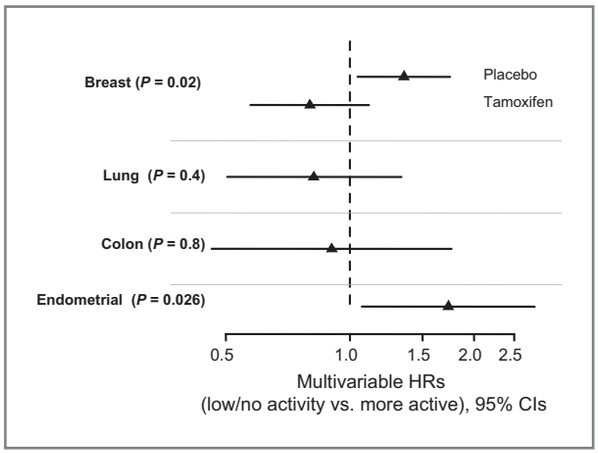


Figure 3. HRs and 95% CIs for the association of physical activity with time to invasive cancer of the breast, lung, colon, and endometrium.

accounted for overweight/obesity (BMI > 25). Results for breast cancer were essentially unchanged (data not shown). Results for physical activity and endometrial cancer, that accounted for overweight/obesity, were suggestive (HR = 1.58; 95% CI, 0.97–2.57; $P = 0.068$).

### Alcohol consumption

The majority of women (8,822, 65.9%) drank in moderation (on average >0 to 1 alcoholic drinks per day); 1,724 (12.9%) drank more; and 2,787 (20.8%) did not drink. In the multivariable models that accounted for treatment, smoking duration, leisure time physical activity, and major risk factors, the risk of breast, lung, and endometrial cancer was not significantly different among alcohol consumption groups ($P = 0.49$, 0.15, and 0.17, respectively; see Fig. 4). The interaction between tamoxifen assignment and alcohol consumption in the analysis of breast cancer was not statistically significant. The risk of colon cancer was significantly different ($P = 0.019$), with lower risk for women who drank in moderation (HR = 0.35; 95% CI, 0.17–0.73) versus nondrinkers. Women who drank more

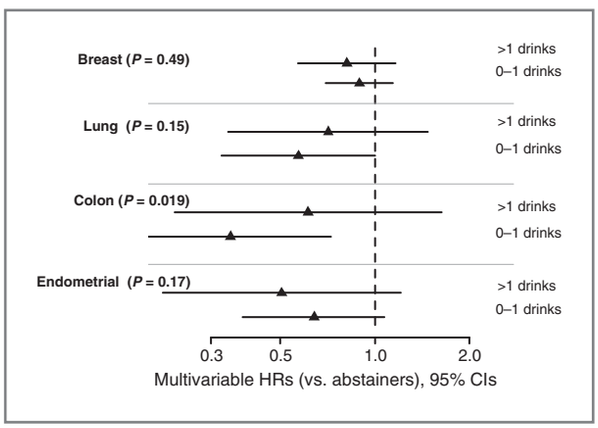


Figure 4. HRs and 95% CIs for the association of alcohol consumption with time to invasive cancer of the breast, lung, colon, and endometrium.

heavily did not have an increased risk of colon cancer (HR = 0.61; 95% CI, 0.23–1.63) relative to nondrinkers. Exploratory analyses compared the risk of breast and colon cancer across higher levels of alcohol consumption (>3 drinks/day) to nondrinkers. Results were nonsignificant, and estimated HRs were <1 (data not shown).

## Discussion

Our understanding of the associations between smoking and the risk of breast cancer has evolved considerably in the past decade. There has been research on this topic for decades, but earlier research had produced equivocal or null results (34, 35), and in 2004 the U.S. Surgeon General concluded that evidence suggested no causal relationship between active smoking and breast cancer (16). However, evidence has emerged from studies over the past decade (2, 36–40), and by 2009 a Canadian expert panel concluded that the relationship between active smoking and breast cancer was consistent with causality (41). Since 2011, additional evidence of association has been reported from 3 large cohort studies. The Women's Health Initiative reported increased breast cancer rates in their population of postmenopausal women although the effect sizes were modest (multivariable HR = 1.09 and 95% CI, 0.97–1.22 for women who smoked 20 to 29 years; and HR = 1.21 and 95% CI, 1.07–1.36 for women who smoked 30 to 39 years vs. never smokers; ref. 3). The Nurses' Health Study also reported higher breast cancer incidence rates with ever smoking and with longer duration of smoking among their population of pre- and postmenopausal women, but the effect sizes and significance levels were again modest (multivariable HR = 1.07 and 95% CI, 1.00–1.14 for women who smoked 20 to 39 years vs. never smokers; ref. 4). The American Cancer Society Cancer Prevention Study II reported HR = 1.26 and 95% CI, 1.00–1.58 for women who smoked 1 to 40 years (9). Based on literature published through October 2012, the U.S. Surgeon General concluded that evidence was "sufficient to identify mechanisms by which cigarette smoking may cause breast cancer," but that evidence was "suggestive but not sufficient to infer a causal relationship between active smoking and breast cancer" (10). The present NSABP P-1 analysis found larger effects for smoking duration than had been seen in those previous studies (e.g., HR = 1.34 and 95% CI, 1.06–1.69 for women who had smoked 15–35 years). We also note that women who were current smokers at baseline in P-1 had a higher estimated risk of breast cancer than never-smokers (HR = 1.32; 95% CI, 0.98–1.78), as did former smokers (HR = 1.24; 95% CI, 0.99–1.54), although smoking status was not statistically significant ($P = 0.074$). Among participants assigned to placebo, the HR was 1.2 (95% CI, 0.8–1.7) for current versus never smokers, and the HR was 1.3 (95% CI, 1.0–1.7) for former versus never smokers (see Supplementary Appendix). These estimates are larger than comparators 1.12 and 1.09 estimated in a recent meta-analysis (9). This might indicate that smoking had an even greater

impact on risk of breast cancer among women in NSABP P-1 than in other studies, perhaps because women in NSABP P-1 were already at an elevated risk of breast cancer because of family history and other factors. For women assigned to tamoxifen, an increased hazard of breast cancer associated with smoking might partly be explained by the decrease in adherence to tamoxifen that was observed among current smokers in P-1 (30).

The evidence for smoking as a risk factor for colon cancer had been inconsistent until recently. A study that examined colon and rectal cancers separately in women found that the risk is largely that of rectal rather than colon cancer (42). A meta-analysis in 2008 demonstrated a pooled relative risk (RR) of colorectal cancers of RR = 1.18 and 95% CI, 1.11–1.25, for ever-smokers versus never-smokers. As in this report, that analysis of cumulative exposure found a significant association only for long-term smoking (more than 30 years; ref. 5). The International Agency for Research on Cancer (IARC) has concluded that tobacco smoking is a cause of colon cancer (43). In contrast to the other 3 cancers examined, smoking may be associated with a decreased risk of endometrial cancer, although our results were not confirmatory in that regard (14).

One strength of NSABP P-1 was the relatively detailed cigarette smoking history assessment. These data permitted analyses using several alternative variables to capture smoking exposure (see Supplementary Appendix). A shortcoming of P-1, typical of trials in cancer prevention and treatment, is that follow-up tobacco use data were not collected. The increasing evidence of the clinical impact of tobacco use on cancer prevention and prognosis across a range of disease sites warrants more widespread assessment in clinical trials than has typically been conducted (10, 29, 44–47). Biochemical validation of smoking status was not conducted in P-1. Validation may not be feasible in many trials, but concern exists that smokers may under-report their tobacco use, particularly in the setting of cancer care delivery (48). Such under-reporting would reduce statistical power to detect associations with tobacco use. Our analysis of breast cancer incidence does not provide evidence of interactions between tamoxifen assignment and smoking; that is, the results do not confirm that tamoxifen is less effective in women who are current smokers or who have more past smoking exposure. The estimated HRs, however, are consistent with a possible modest interaction.

The U.S. Department of Health and Human Services (DHHS) Physical Activity Guidelines Committee concluded that active women have a reduced risk of breast and colon cancer, and may also have a reduced risk of lung cancer (49). However, the associations were complex. For example, some of the studies they reviewed had reported that the association between physical activity and breast cancer risk is weaker in women with a family history of breast cancer. We found that leisure-time physical activity was associated with decreased risk of breast cancer, but that this association was limited to women assigned to placebo. That interaction between treatment and physical activity would need to be replicated in other studies. We did not detect significant increases in risk of colon or lung cancer with low physical activity. Our results might differ from the DHHS report because of the limitations of our data: physical activity was self-reported, using broad measures, reported only at baseline, and was most often at levels that may have been below the thresholds that past studies have found associated with improvement in cancer risk (see the "Physical Activity and Cancer Factsheet" on www.cancer.gov). We did confirm a previously reported protective effect of physical activity on endometrial cancer. That association seems to be partly mediated by obesity because when obesity was included in the model, the significance of physical activity was diminished.

Past studies have indicated an increased risk of breast and colon cancer with heavy alcohol consumption (50, 51). With respect to breast cancer, a reanalysis of data from 53 epidemiologic studies found elevated risk among women who drank 3 to 3.5 drinks per day (RR = 1.32; 95% CI, 1.19–1.45) or more (RR = 1.46; 95% CI, 1.33–1.61) versus nondrinkers (35). A review found that the increase in risk was for hormone receptor-positive, and not for hormone receptor-negative, breast cancers (52). IARC concluded that there was sufficient evidence that alcohol was causally related to female breast cancer (51). A recent meta-analysis found an increased risk even for women classified as light drinkers (up to 1 drink per day) versus nondrinkers, but the increase was small (pooled RR = 1.03; 95% CI, 1.00–1.07 adjusted for major risk factors; ref. 50). A large cohort study also reported increased risk for moderate levels of alcohol drinking (RR = 1.15; 95% CI, 1.06–1.24 for women who drank roughly 1/3–2/3 drinks per day; ref. 53). With respect to colon cancer, a pooled analysis of 8 cohort studies in the United States and Europe demonstrated a RR of 1.45 for colon cancer among people who consumed at least 3 drinks per day on average (54). However, the same study found a slight decrease in risk of colon cancer that almost reached statistical significance (RR = 0.92; 95% CI, 0.84–1.01) among the lightest drinkers (0–5 g of alcohol per day, or roughly one third of one drink) relative to nondrinkers. A European cohort study found significantly increased risk of colon cancer only at levels of alcohol consumption above 4 drinks per day, and no increased risk of colon cancer with modest drinking (55). Our results for alcohol consumption show decreased risk for all 4 cancer sites, with significant decreases only for colon cancer. NSABP P-1 included few women who reported drinking at very high levels (129 and 94 women who drank 3 to 4, or more than 4 drinks per day, respectively). Furthermore, women classified as drinking up to one drink per day actually drank very modestly, with a median of 0.13 drinks per day. Therefore, our data do not necessarily constitute evidence against past studies, which found increased risk at high levels of alcohol consumption and either no increase or small increases in risk among those who drink in moderation.

Differences between results from NSABP P-1 and other studies may be because of the systematic prospective detection of cancers at all organ sites, to the unique population in NSABP P-1, or to statistical variation. Our findings must be interpreted within the context of the special characteristics of the women who volunteered for this clinical trial in the early 1990s. Women in NSABP P-1 differed from the general population by definition, having been selected based on their elevated risk of breast cancer. They had to perceive themselves as being at very high risk for breast cancer to consider enrolling in what may have seemed a risky study, in which healthy women were taking a drug used for the treatment of cancer. Second, if a woman considered herself at high risk for breast cancer and was willing to enter this clinical trial, she had to accept the 50% chance that she would be given a placebo. Third, the demographic characteristics of the women who volunteered reflected a higher socioeconomic status and highly educated population, typically less likely to have unhealthy behaviors. For example, they were less likely to smoke cigarettes than women of a comparable age during the 1990s. In the 1992 National Health Interview Survey (NHIS), of adult women of age >65, 12.9% reported smoking cigarettes either every day or some days; of women age >65 enrolling in NSABP P-1 in the same year, only 6.4% were current smokers (56). For women of ages 45 to 64 years, the rates were 26.5% in the NHIS versus 13.3% in NSABP P-1. And, as noted above, participants were not heavy alcohol consumers. Thus, conclusions that we make about behaviors and their influence on cancer risk should be interpreted in the context of this unique population. In addition, a strength of our analysis is that we included the major known risk factors for each cancer in the multivariable models, which may not have been possible in some prior research.

These new findings contribute to the growing evidence base and provide a richer understanding of the complex impact of risk behaviors of cigarette smoking, alcohol consumption, and physical activity on primary cancer incidence. Our findings indicate that women who are at elevated risk of breast cancer, because of family history or other risk factors used for NSABP P-1 eligibility, should have their smoking status and physical activity assessed by their health care providers. Results indicated higher risks of breast, lung, and colon cancers with higher intensity and/or duration of smoking, and with lower baseline leisure-time physical activity, which suggests that smoking cessation and an increase in physical activity may provide a reduction in risk. Our study therefore provides further support that smoking cessation and regular physical activity are important means to reduce cancer risk. Those who smoke or are inactive, should be informed, encouraged, and assisted in behavioral change to reduce the risk of cancer.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** S.R. Land
**Development of methodology:** S.R. Land
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** D.L. Wickerham, J.P. Costantino
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** S.R. Land, Q. Liu, J.P. Costantino, P.A. Ganz
**Writing, review, and/or revision of the manuscript:** S.R. Land, D.L. Wickerham, J.P. Costantino, P.A. Ganz
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** S.R. Land, Q. Liu, J.P. Costantino
**Study supervision:** D.L. Wickerham, P.A. Ganz

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