**REVISED MANUSCRIPT**

# A Prospective Study of Bowel Motility and Related Factors on Breast Cancer Risk

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ABSTRACT

Background: Estrogen is an established risk factor for breast cancer. Greater bowel motility has been associated with increased estrogen excretion and lower serum estrogen levels, suggesting it may influence breast cancer risk. However, only one other epidemiologic study thus far, to our knowledge, has examined the relation between bowel motility and breast cancer risk.

Methods: We prospectively examined whether bowel motility, measured by self-reported frequency of bowel movements, and related factors (constipation, laxative use, water consumption, and dietary fiber intake) were associated with incidence of breast cancer among 28,586 postmenopausal women, aged 50-76, in the Vitamins And Lifestyle (VITAL) study. Cox proportional hazards models were used to estimate multivariate-adjusted relative risks (RR) and 95% confidence intervals (CI). From 2000-2005, 507 incident invasive breast cancers among the cohort were identified.

Results: Women with very frequent (≥ 3/day) bowel movements had a 46% decreased risk compared to 1/day women (RR = 0.54, 95% CI = 0.31 to 0.92), but the test for linear trend was not significant ($P_{trend}$=0.41). Constipation was nonsigificantly associated with increased risk (RR = 1.30 for ≥ 1/week versus <1/year, 95% CI = 0.87 to 1.95). No statistically significant associations were observed for the other study exposures: 10-year chemical laxative use, 10-year use of fiber laxatives, water consumption, and dietary fiber intake.

Conclusion: This study adds limited support to the hypothesis that increased bowel motility lowers breast cancer risk.

## Introduction

Estrogen is strongly implicated in breast cancer etiology (1), and exposures that increase estrogen excretion may plausibly decrease breast cancer risk. Estrogen is mainly metabolized in the liver, where glucuronidation and sulfation make estrogen more water-soluble for excretion via urine and the stool from bile (2). Bile contains approximately 50% of all estrogen metabolites produced and, although most of the estrogen is reabsorbed via enterohepatic circulation, about 7% of estrogen is excreted (3).

Experimental studies suggest that greater bowel motility lowers estrogen levels (4, 5) potentially enough to reduce risk. However, only one other epidemiologic study, to our knowledge, has examined bowel motility and breast cancer risk, and results were inconclusive, with less than 130 cases (6). We, thus, prospectively examined whether bowel motility, measured by frequency of bowel movements, and related factors (constipation, laxative use, water consumption, and dietary fiber intake) were associated with incidence of postmenopausal breast cancer.

## Methods

Study Population

Participants were women in the Vitamins and Lifestyle (VITAL) cohort study. VITAL was initiated between 2000-2002, when 37,382 men and 40,337 women, aged 50-76 years and living in western Washington State, answered a 24-page self-administered questionnaire about their health history and cancer risk factors (7).

Women were excluded if they had, at baseline, a history of breast cancer (n=3,164), were premenopausal or had missing menopausal status (n=1921), never had a period (n=22), or had missing mammography data (n=75). Women were considered postmenopausal if they reported a natural menopause, had ever used postmenopausal hormones (PMH) for at least a year, had bilateral oophorectomy with or without hysterectomy, or were 60 years or older at baseline. Age at menopause was assigned as the age menstrual periods ended naturally or by bilateral oophorectomy or age at first use of PMH, whichever came first. Women who reported hysterectomy without bilateral oophorectomy were considered to be postmenopausal if they were over age 55 or had ever used PMH; otherwise, their menopausal status was unknown. For those women, age at menopause was considered to be the age they first used PMH , otherwise it was set to missing.

We additionally excluded women who reported conditions known to seriously affect bowel functioning: stomach cancer (n=25), colorectal cancer (n=409), pancreatitis (n=347), ulcerative colitis or Crohn's disease (n=540), removal of gallbladder (n=5,092), or gastrointestinal procedures (n=15) (e.g. intestinal bypass, ileum resection, etc.). During follow-up, 141 women subsequently diagnosed with *in situ* breast cancer were also excluded. Thus, 28,586 postmenopausal women remained.

Baseline Questionnaire

Participants were asked "how often do you usually have a bowel movement?"; the choices were <1 /week, 2-4/week, 5-6/week, 1/day, 2/day and ≥3 /day. For constipation, participants indicated how often they felt sufficiently constipated over the past 10 years to need some intervention (i.e., laxative, enema, or prunes). The five choices ranged from <1/year to ≥ 1/week. We further queried women about their 10-year use of chemical laxatives (i.e., Ex –lax, Correctol, milk of magnesia), with responses ranging from <1/year to ≥ 1/week. For laxatives containing fiber (i.e., Metamucil, Citrucel, FiberCon, or Fiberall), we calculated 10-year average use by multiplying years of use with days/week and dividing by 10 years.

A food frequency questionnaire (FFQ), adapted from the Women's Health Initiative and other studies (8-10),was used to ascertain intakes of water, dietary fiber, and other nutrients (including alcohol). Participants reported their usual frequency and portion size of 120 foods and beverages consumed during the previous year. Total water intake represented consumption from tap/bottle plus estimated water content from foods/beverages. We used the nutrient database, Minnesota Nutrient Data System for Research (University of Minnesota's Nutrition Coordinating Center, Minneapolis, MN), to obtain estimated nutrient intakes (11). Participants were excluded from nutrient analyses if they left a FFQ page blank or if their reported total energy intake was <600 kcal or >4000 (n=3001).

The 3-month test-retest reliability (12) of our exposures was examined among 75 VITAL women. Kappa coefficients were 0.67 for bowel movement frequency, 0.76 for constipation, 0.72 for chemical laxatives, and 0.59 for fiber-containing laxatives. Intraclass correlation coefficients were 0.57 for total water consumption and 0.75 for total dietary fiber intake. Frequency of bowel movements has been negatively correlated with gastrointestinal or colonic transit time, and may be a reasonable proxy of bowel function (13-15).

Previous publications describe baseline assessment and calculation of alcohol intake in the past-year (16), physical activity (17), BMI (17), fruit and vegetable consumption (18), and multivitamin intake (7). PMH use was computed from questions about prescription estrogen and progestin as pills or patches,

excluding oral contraceptives. PMH use for <1 year was considered never use. Total intakes of vitamin C, magnesium, calcium, and iron (which may influence bowel motility (19)) were calculated by adding intakes from dietary sources with averaged 10-year consumption from supplements.

Outcome

Incident breast cancer cases and information on stage and other tumor characteristics were obtained through annual linkage to the SEER cancer registry (7). Among eligible women, we identified 507 invasive breast cancer cases, diagnosed between October 2000 and December 2005.

Statistical Analysis

Cox proportional hazards models were used to estimate age- and multivariate-adjusted relative risks (RR) and 95% confidence intervals (CI) for breast cancer risk. Age was treated as the time variable. Censor date was defined as the earliest date of: withdrawal from the study (0.04%); death (2.7% as ascertained from Washington State death files); move out from 13 county catchment area of the SEER registry (4.3% as identified by linkage to the National Change of Address System or other follow-up procedures); or end of follow-up (December 31, 2005). For the bowel motility exposure, we chose 1/day as the referent because almost half of the women reported this frequency and there were fewer women in the extremes. We adjusted for established risk factors for breast cancer (Table 2, footnote). Further adjustment for intakes of multivitamin in the past 10-years, total energy, fruit and vegetables, vitamin C, magnesium, calcium, and iron did not change results so these factors were not included our final models. Tests for linear trend were performed by modeling exposures ordinally.

To examine effect modification, we collapsed bowel motility into 3 exposure categories and used stratified analyses. Wald tests of the interaction term were used to test for interaction. We tested whether risk estimates by subgroups of hormone-receptor status statistically differed by excluding all non-cases and fitting a multivariate unconditional logistic regression model comparing the two case groups of interest. Analyses were performed using SAS, version 9.1, (SAS Institute Inc., Cary, NC).

**Results**

Participants were, on average, 61 years (range 50-76). Women with more bowel movements were older, were more likely to have an early age at menarche (<12 years), be nulliparous, have a greater BMI and generally have higher dietary and nutrient intakes (Table 1). Women in the lowest category of bowel movement frequency (≤4/week) were the least physically active. With respect to bowel motility and our other exposures (Table 1), as expected, women with more frequent bowel movements were less likely to be constipated and use chemical laxatives and more likely to consume water. However, we observed no association between bowel frequency and intakes of fiber-containing laxatives or dietary fiber.

Frequent bowel movements (≥ 3/day) were significantly associated with decreased breast cancer risk compared to once a day (RR = 0.54, 95% CI = 0.31-0.92), but the test for trend was not statistically significant (*P* trend = 0.41) (Table 2). If we combined the two less frequent bowel movement groups into the reference group, the RRs were similar (RR=0.57 for ≥3/day vs. ≤1/day; 95% CI= 0.33-0.97), and there was a significant test for trend across the 3 groups (*P* trend =0.02). There was a nonsignficant increased breast cancer risk among women with frequent constipation (RR = 1.30 for ≥ 1/week versus <1/year, 95% CI = 0.87-1.95). We did not find associations for the other study exposures (Table 2).

BMI and PMH provide a source of endogenous or exogenous estrogen, respectively. However, we did not observe effect modification of the bowel motility-breast cancer relation by BMI (<25 kg/m$^2$ and ≥ 25 kg/m$^2$ , *P* interaction = 0.91) or PMH use (≤ 4 years and > 4 years, *P* interaction = 0.85 ). Nor did we observe differential effects of bowel motility by estrogen receptor (ER) status (*P* interaction for difference between ER+ versus ER-= 0.78) or progesterone receptor (PR) status (*P* interaction for difference between PR+ versus PR- = 0.23).

**Discussion**

This large prospective investigation provides modest support for an association between bowel motility and breast cancer risk. We observed a 46% decrease in breast cancer risk among women reporting very frequent (≥ 3/day) bowel movements than those reporting 1/day, but no evidence for a linear trend across all five exposure categories. Furthermore, there was a small, statistically nonsignificant 30% increased breast cancer risk among women reporting frequent constipation.

We know of only one study reporting on bowel motility and breast cancer risk (6). NHANES I (6), reported a nonsignificant increase in breast cancer risk for infrequent bowel movements (RR = 1.5 for ≤ 4/week versus >1/day, 95% CI = 0.80-2.70) and a borderline statistically significant increased risk for firm stool consistency (RR = 1.8 for firm versus normal, 95% CI = 1.0 - 3.2). Furthermore, there was a suggestion of a decreased association for diarrhea (RR = 0.6 versus no bowel problems, 95% CI = 0.2 - 1.9). Our results are consistent with these in suggesting some relationship between bowel motility and breast cancer risk. Furthermore, NHANES I, like ours, did not detect an association between laxative use and breast cancer risk but, it had limited power (6). For water consumption, we know of only one hospital-based case-control study (20); it observed a strong inverse association with breast cancer risk (RR = 0.21 for intake of any water versus none, 95% CI = 0.07 - 0.62), however, recall and selection biases were potentially issues. Most cohort investigations have not observed decreased risks for total dietary fiber (reviewed in (21)). Possibly high-fiber intakes (≥ 30 g/d) are relevant, but <5% of our participants met this level.

Experimental and observational data provide compelling biological evidence that frequent bowel motility is associated with increased excretion of estrogen in the stool and lower serum estrogen levels. Diet supplemented with wheat or oat bran, which are generally associated with greater amount of stool excreted, increased fecal estrogen concentrations in animal and human trials (22, 23). In a crossover trial among women, fiber supplementation and separately, senna (a chemical laxative), reduced whole-gut transit time, increased frequency of bowel movements, and improved stool consistency compared to baseline.(4) These treatments also lowered serum estrogen (estrone, non-protein-bound estrone, and/or

estrone sulfate) concentrations ~10% to 18% - magnitudes potentially relevant for breast cancer risk. Women given loperamide, a drug which slows transit, showed no such changes in serum estrogen levels (4). Among observational studies, women with higher stool weight (vegetarians and recent Asian immigrants) tended to have greater fecal estrogen concentrations and lower plasma estrogen levels than those with lower stool weight (24-26). Conversely, severe constipation (decreased bowel motility) has been associated with greater cellular abnormalities in nipple aspirates and among case reports, has been linked with breast abnormalities (27). To date, the most relevant parameter(s) of bowel motility effecting estrogen concentration are unknown.

Strengths of our study include its prospective design, our ability to control for a variety of risk factors for breast cancer, and our exclusion of several medical conditions that can affect bowel motility. Study limitations include use of self-reported exposures. Although our exposures were sufficiently reproducible, nondifferential measurement error would have attenuated associations. More specific measures of bowel function such as gastrointestinal transit time, stool weight, and stool consistency (which have been associated, as discussed above, with changes in estrogen levels) and of functional constipation would improve the ability to understand the effect of bowel function on breast cancer risk. In addition, case numbers in the highest non-dietary exposure categories in this study were small, limiting our power.

In conclusion, our limited results, in conjunction with previous mechanistic evidence and one epidemiologic study, provide some support to the hypothesis that increased bowel motility lowers breast cancer risk. Future studies with more accurate exposure measures are needed to confirm this association.

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**Table 1. Baseline characteristics* according to categories of bowel movement frequency among women in VITAL cohort †**

| | Bowel Movement Frequency | | | | |
|---|---|---|---|---|---|
| | ≤4/week | 5-6/week | 1/day | 2/day | ≥3/day |
| Number of participants | 3594 | 4857 | 13201 | 5583 | 1260 |
| **Demographics** | | | | | |
| Age (years) | 60.7 | 61.3 | 62.2 | 62.0 | 62.4 |
| White (%) | 90.4 | 93.0 | 90.8 | 90.8 | 91.2 |
| **Family history /breast-related procedures** | | | | | |
| Mother or sister with breast cancer (%) | 14.7 | 15.2 | 14.8 | 15.2 | 15.0 |
| Mammography in past 2 years (%) | 91.7 | 92.8 | 90.7 | 89.8 | 89.9 |
| Breast biopsy (%) | 18.7 | 18.6 | 17.5 | 18.2 | 18.1 |
| **Reproductive factors** | | | | | |
| Age at menarche (% <12 years) | 17.2 | 17.3 | 17.0 | 18.7 | 21.0 |
| Nulliparous (%) | 11.6 | 12.5 | 13.4 | 13.7 | 13.9 |
| Age at first birth ‡ (years) | 22.9 | 23.5 | 23.5 | 23.4 | 23.2 |
| Parity ‡ (number of births) | 2.7 | 2.7 | 2.6 | 2.7 | 2.7 |
| Age at menopause (years) | 47.2 | 47.8 | 47.9 | 47.6 | 46.7 |
| Ever use of estrogen plus progestin PMH (%) | 33.7 | 38.0 | 36.6 | 36.3 | 35.6 |
| **Lifestyle/ anthropomorphic factors** | | | | | |
| Current BMI (kg/m$^2$) | 26.2 | 26.1 | 26.5 | 27.8 | 27.8 |
| Height (in) | 64.8 | 64.9 | 64.7 | 64.5 | 64.6 |
| Total physical activity (MET-hour/week) | 8.4 | 9.6 | 9.9 | 9.2 | 9.3 |
| Current cigarette smoking (%) | 8.6 | 6.5 | 8.5 | 7.6 | 8.6 |
| **Dietary factors** | | | | | |
| Total energy intake (kcal/day) | 1398 | 1445 | 1487 | 1580 | 1626 |
| Alcohol (g/day) | 4.3 | 5.5 | 5.5 | 5.7 | 6.0 |
| Dietary fat (% energy) # | 33.3 | 32.4 | 32.4 | 32.5 | 32.8 |
| Dietary carbohydrate (% energy) # | 49.1 | 49.6 | 49.8 | 49.8 | 49.4 |
| Fruit and vegetable consumption (servings/day) | 3.87 | 4.30 | 4.54 | 4.86 | 4.84 |
| Multivitamin use (any use over 10 years %) | 66.1 | 70.4 | 71.1 | 73.4 | 73.5 |
| Total vitamin C (mg/day) §, # | 315 | 345 | 366 | 408 | 445 |
| Total magnesium (mg/day) §, # | 312 | 330 | 337 | 348 | 357 |
| Total calcium (mg/day) §, # | 1062 | 1111 | 1147 | 1177 | 1195 |
| Total iron (mg/day) §, # | 18.0 | 18.7 | 18.8 | 19.3 | 19.8 |
| **Study exposures** | | | | | |
| Constipation, any report over year (%) | 58.3 | 40.7 | 27.7 | 21.2 | 21.3 |
| Chemical laxatives, any report of use over 10 years (%) | 35.1 | 21.3 | 13.2 | 9.8 | 9.5 |
| Fiber laxatives, any report of use over 10 years (%) | 19.4 | 15.5 | 11.6 | 13.6 | 17.8 |
| Total water intake from foods and beverages (g/day) | 2415 | 2520 | 2577 | 2691 | 2758 |
| Water intake from tap/bottle (8oz servings/day) | 3.5 | 3.7 | 3.8 | 4.1 | 4.2 |
| Total (insoluble and soluble) fiber from diet (g/day) # | 14.3 | 15.2 | 15.4 | 15.6 | 15.3 |
| Insoluble fiber from diet (g/day) # | 10.5 | 11.2 | 11.3 | 11.5 | 11.2 |

* Age adjusted means or percentages of baseline characteristics were calculated by standardizing to the age distribution of the study population.

† 5% or less had missing data for characteristics - exceptions were for age at menopause (9% missing), parity (8% missing),BMI (6% missing), and intakes of diet (~9% missing).

‡ Among parous women only.

§ Intake from dietary plus supplemental sources.

\# Energy-adjusted nutrient intakes.

**Table 2. Relative risk (RR) of breast cancer by bowel movement frequency, constipation, and intakes of laxatives, water and dietary fiber, VITAL cohort**

| | Cohort No. (%) | | Cases No. (%) | | Age-adjusted RR (95% CI) | Multivariate-adjusted RR* (95% CI) |
|---|---|---|---|---|---|---|
| Bowel movement frequency | | | | | | |
| ≤4/week | 3594 | (13) | 55 | (11) | 0.81 (0.61 - 1.09) | 0.84 (0.63 - 1.12) |
| 5-6/week | 4857 | (17) | 82 | (16) | 0.88 (0.69 - 1.13) | 0.87 (0.68 - 1.11) |
| 1/day | 13201 | (46) | 264 | (52) | 1.00 | 1.00 |
| 2/day | 5583 | (20) | 92 | (18) | 0.83 (0.65 - 1.05) | 0.81 (0.64 - 1.02) |
| ≥3/day | 1260 | (4) | 14 | (3) | 0.56 (0.33 - 0.95) | 0.54 (0.31 - 0.92) |
| *P* trend † | | | | | | 0.41 |
| Constipation | | | | | | |
| <1/year | 19013 | (67) | 332 | (67) | 1.00 | 1.00 |
| 1-4/year | 4930 | (17) | 89 | (18) | 1.02 (0.81 - 1.29) | 1.02 (0.80 - 1.28) |
| 5-11/year | 1833 | (6) | 27 | (5) | 0.83 (0.56 - 1.23) | 0.83 (0.56 - 1.23) |
| 1-3/month | 1248 | (4) | 22 | (4) | 1.00 (0.65 - 1.53) | 1.02 (0.66 - 1.57) |
| ≥1/week | 1186 | (4) | 26 | (5) | 1.24 (0.83 - 1.84) | 1.30 (0.87 - 1.95) |
| *P* trend † | | | | | | 0.55 |
| Chemical laxative use (past 10 years) | | | | | | |
| <1/year | 22243 | (83) | 401 | (85) | 1.00 | 1.00 |
| 1-4/year | 2823 | (10) | 39 | (8) | 0.76 (0.54 - 1.05) | 0.75 (0.54 - 1.05) |
| ≥5/year | 1885 | (7) | 32 | (7) | 0.93 (0.65 - 1.33) | 0.96 (0.67 - 1.38) |
| *P* trend † | | | | | | 0.35 |
| Fiber laxative use (past 10 years) | | | | | | |
| <1 days/week | 25177 | (89) | 439 | (88) | 1.00 | 1.00 |
| 1-2 days/week | 1829 | (6) | 32 | (6) | 0.97 (0.68 - 1.39) | 0.95 (0.66 - 1.36) |
| ≥3 days/week | 1265 | (4) | 30 | (6) | 1.30 (0.90 - 1.88) | 1.27 (0.87 - 1.84) |
| *P* trend † | | | | | | 0.35 |
| Total water intake from tap/bottle, foods and beverages (range, 8 oz cups/day) | | | | | | |
| 1st Q (<8.4) | 6361 | (25) | 105 | (23) | 1.00 | 1.00 |
| 2nd Q (8.4-<11.0) | 6432 | (25) | 113 | (25) | 1.08 (0.82 - 1.41) | 1.04 (0.79 - 1.36) |
| 3rd Q (11.0-<13.9) | 6439 | (25) | 114 | (25) | 1.09 (0.83 - 1.44) | 1.03 (0.78 - 1.36) |
| 4th Q (13.9-<44.1) | 6353 | (25) | 123 | (27) | 1.22 (0.91 - 1.63) | 1.16 (0.86 - 1.56) |
| *P* trend ‡ | | | | | | 0.36 |
| Water intake from tap/bottle only (range, 8 oz cups/day) | | | | | | |
| 1st Q (<2.3) | 6460 | (25) | 103 | (23) | 1.00 | 1.00 |
| 2nd Q (2.3-≤3.5) | 6521 | (25) | 117 | (26) | 1.14 (0.87 - 1.48) | 1.12 (0.86 - 1.46) |
| 3rd Q (3.5 -<6.0) | 4906 | (19) | 87 | (19) | 1.09 (0.82 - 1.46) | 1.08 (0.81 - 1.45) |
| 4th Q (6.0-9.0) | 7698 | (30) | 148 | (33) | 1.23 (0.95 - 1.58) | 1.23 (0.95 - 1.58) |
| *P* trend ‡ | | | | | | 0.15 |
| Total dietary fiber (range, g/day) | | | | | | |
| 1st Q (<10.5) | 6249 | (24) | 114 | (25) | 1.00 | 1.00 |
| 2nd Q (10.5-<14.7) | 6385 | (25) | 99 | (22) | 0.83 (0.63 - 1.09) | 0.86 (0.65 - 1.14) |
| 3rd Q (14.7-<19.8) | 6422 | (25) | 114 | (25) | 0.95 (0.72 - 1.27) | 0.99 (0.74 - 1.32) |
| 4th Q (19.8-58.3.7) | 6529 | (26) | 128 | (28) | 1.05 (0.76 - 1.44) | 1.14 (0.82 - 1.60) |
| *P* trend ‡ | | | | | | 0.32 |
| Insoluble dietary fiber (range, g/day) | | | | | | |
| 1st Q (<7.7) | 6231 | (24) | 117 | (26) | 1.00 | 1.00 |
| 2nd Q (7.7-<10.7) | 6399 | (25) | 93 | (20) | 0.75 (0.57 - 1.00) | 0.78 (0.59 - 1.03) |
| 3rd Q (10.7-<14.6) | 6412 | (25) | 118 | (26) | 0.95 (0.72 - 1.26) | 0.98 (0.74 - 1.31) |
| 4th Q (14.6-44.2) | 6543 | (26) | 127 | (28) | 1.00 (0.73 - 1.36) | 1.07 (0.78 - 1.49) |
| *P* trend ‡ | | | | | | 0.39 |

Abbreviation, Q= quartile.

* Controlled for: age, race, mother/sister with breast cancer, mammography within two years preceding baseline, history of breast biopsy, age at menarche, age at first birth, age at menopause, combined estrogen and progestin PMH use, BMI at baseline, past-year alcohol intake, height, and physical activity in past 10 years. For water and dietary fiber analyses, total energy intake (kcal/day) was included.

† Test for trend calculated using ordinal term of above exposure categories.