

Phenolphthalein-containing Laxative Use in Relation to Adenomatous Colorectal Polyps in Three Studies

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Phenolphthalein, the active ingredient in many laxatives, was recently found to be a carcinogen in animal models. Human data suggest a laxative-colon cancer association, but few data specifically address the effects of phenolphthalein-containing laxatives. We examined use of phenolphthalein-containing laxatives in relation to occurrence of adenomatous colorectal polyps in data from three case-control studies. The study conducted in Los Angeles, California (1991-1993), and the two studies conducted in North Carolina (1988-1990 and 1992-1995) altogether included 866 cases and 1,066 controls. The prevalence of using phenolphthalein-containing laxatives at least once a week in the recent past, however, was less than 5% among these subjects. The multivariate-adjusted odds ratios associated with recent use of phenolphthalein-containing laxatives once a week or more were 1.8 [95% confidence interval (CI), 0.5-6.2] in Los Angeles, 1.0 (CI, 0.4-2.2) in North Carolina (1988-1990), and 1.1 (CI, 0.2-5.7) in North Carolina (1992-1995). For use of other types of laxatives, the corresponding odds ratios were 1.3 (CI, 0.9-1.9) in Los Angeles, 1.0 (CI, 0.5-1.7) in North Carolina (1988-1990), and 0.9 (CI, 0.4-1.8) in North Carolina (1992-1995). Although the low prevalence of frequent use made for relatively wide confidence intervals, overall these data suggest that use of phenolphthalein-containing laxatives does not increase risk of adenomatous colorectal polyps. *Key words:* adenomatous, case-control studies, cathartics, colorectal neoplasms, pharmacoepidemiology, phenolphthaleins, polyps.

Environ Health Perspect 105:1210-1212 (1997). <http://ehp.niehs.nih.gov>

Phenolphthalein, the active ingredient in many laxatives, was recently found to be a multisite/multispecies carcinogen in animals (1). In some of the animal experiments, the dose of phenolphthalein (per unit body surface area) found to be carcinogenic was within an order of magnitude of that prescribed for humans. Although colorectal neoplasia in animals was not observed, a link between laxative use and colorectal cancer in humans has been reported (2). Because of the finding that phenolphthalein is a carcinogen and because of the association of laxative use with risk of colorectal cancer, we hypothesized that use of phenolphthalein-containing laxatives increases risk of adenomatous colorectal polyps. Colorectal adenomas are precursors of colorectal cancer (3,4), and adenomas and cancer of the large bowel have many risk factors in common (5,6). In three recent case-control studies of risk factors for adenomatous colorectal polyps, laxative use was ascertained, thus providing a means by which to test the hypothesis.

Methods

The data considered in this report come from a case-control study conducted in Los Angeles, California, in 1991-1993 and two studies conducted in North Carolina in 1988-1990 and 1992-1995. Details of each study are presented elsewhere (7-10). In all

three studies, subjects were selected from among those undergoing an endoscopic procedure at designated medical facilities (Table 1). All cases had histologically confirmed adenomatous polyps. Controls in Los Angeles had no polyps of any type and in North Carolina, controls had no adenomatous polyps. Controls in Los Angeles were individually matched to cases by age, sex, medical facility, and period of exam; controls in North Carolina were not matched to cases. In all three studies, subjects were excluded if they had previous bowel cancer or adenoma, bowel surgery, inflammatory bowel disease, polyposis, or could not speak English. Subjects with colitis due to radiation or infection were excluded in North Carolina. In Los Angeles and in the second North Carolina study (North Carolina-2), subjects were free of invasive cancer, whereas in the first North Carolina study (North Carolina-1), 27 subjects with colorectal cancer were included in the case group. Other differences were that in Los Angeles subjects had to be residents of Los Angeles or Orange County, and in North Carolina subjects had to have a satisfactory bowel preparation and a complete endoscopy. The lower response rate in the second North Carolina study as compared with the first was because the protocol included a rectal biopsy and blood draw. Informed consent was obtained from all participants.

In all three studies, subjects provided information about themselves after the endoscopy. Dietary data were collected in Los Angeles using a self-administered food-frequency questionnaire (11); dietary data were collected in North Carolina over the phone using a similar instrument (12). Data on laxative use and other nondietary variables were collected by personal interview in Los Angeles and over the telephone in North Carolina. In Los Angeles, subjects were asked, "In the year before your sigmoidoscopy, did you take any of the following substances at least once a week, to maintain regular bowel movements?" The list of laxatives read to the subjects contained no phenolphthalein-containing laxatives, but included the category other laxative preparations. If the subject reported use of a laxative in this category, the preparation was recorded. For each agent reported, the number of days per week used and the total number of years of use was ascertained. In North Carolina, subjects were asked "How often do you take laxatives?" and "Which laxative do you take most often?" In all studies, the responses to questions about the preparation used were reviewed without knowledge of subjects' case-control status, and laxatives were classified as containing phenolphthalein if one of the following brands was reported: Agoral, Alophen, Colax, Correctol, Dialose, Doxidan, Espotabs, Evac-U-Gen, Evac-U-Lax, Ex-Lax, Feen-A-Mint, FemiLax, Kondremul, LaxCaps, Lax-Pills, Medilax, Modane, Phenolax, or Prulet (13). In the Los Angeles study, questions about constipation were not asked; however, frequency of bowel movements in the year before sigmoidoscopy was ascertained. In the North Carolina studies, subjects were asked: "Are you ever constipated?" as well as a question about frequency of bowel movements.

Results from logistic regression models adjusted for selected *a priori* potentially confounding factors are presented (see Table 3 for list of covariates). For the Los

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This work was supported in part by grants from the National Institutes of Health (CA66635 and CA44684).

Received 5 May 1997; accepted 13 August 1997.

Angeles data, adjustment for smoking accounted for most of the difference between the crude and adjusted odds ratios (2.3 vs. 1.8); in the second North Carolina study, age accounted for most of the difference (1.6 vs. 1.1). Additional adjustment for race, body mass index, or use of non-steroidal anti-inflammatory agents (the latter was available for Los Angeles and the second North Carolina study) had no important effect on the results. The pair matching in Los Angeles was retained in the analysis by use of conditional models. We chose not to pool the results because we thought colonoscopy- and flexible sigmoidoscopy-based study results would not be strictly comparable, due to the possibility that controls in the sigmoidoscopy-based study might have right-sided polyps. Further, the differences between the North Carolina studies described above supported the separate presentation of results.

Results

With subjects from each study categorized according to whether phenolphthalein-containing laxatives were used at least once a week (Table 2), the overall prevalence of use was 1.3% in Los Angeles, 4.2% in North Carolina-1, and 2.3% in North Carolina-2. Consequently, cell counts were small and confidence intervals were wide (Table 2). Nonetheless, a consistent association of phenolphthalein-containing laxative use with risk of polyps was not present. Use of other laxatives was not associated with risk. Adjustment of results for dietary factors had little effect on results; thus, only the fully adjusted odds ratios are shown.

More detailed analyses revealed little else of importance. In the Los Angeles data, we examined frequency of use; the adjusted odds ratio was 1.2 (CI, 0.7–2.1) for each day per week a phenolphthalein-containing laxative was used. The adjusted odds ratio per 10 years of use of phenolphthalein-containing laxative was 0.7 (CI, 0.1–3.6), and the adjusted odds ratio per 50 times a phenolphthalein-containing laxative was taken was 1.0 (CI, 0.9–1.1). In neither North Carolina study was frequency of use related to risk. The adjusted odds ratio for each day per week a phenolphthalein-containing laxative was used was 1.0 (CI, 0.9–1.1) in both studies. The North Carolina-2 data were too sparse to allow an assessment of site-specific effects for phenolphthalein-containing laxatives. The North Carolina-1 data suggested no predilection for an association on either side of the large bowel.

In Los Angeles, the adjusted odds ratio for having a bowel movement more than 7 times/week, as compared to less than 7

Table 1. Characteristics of the three studies

Attribute	Study		
	Los Angeles	North Carolina-1	North Carolina-2
Dates subjects enrolled	1991–1993	1988–1990	1992–1995
Endoscopy Type	Sigmoidoscopy	Colonoscopy	Colonoscopy
Indication (%) ^a	Screening (45) Minor symptoms (15) Not stated (41)	Bleeding (57) Anemia (10) Other (33)	Bleeding (35) Anemia (8) Other (57) ^b
Cases (n)	488	236	142
Controls (n)	488	409	169
Age range (years)	50–74	30–89	30–88
Mean age (years)	62	60	59
Sex (% female)	34	58	53
Response rate (%)	83	83	45

^aTotals do not equal 100% for Los Angeles due to rounding.

^bAmong the other indications, the most frequent was follow-up for a previous nonadenomatous polyp (17.4%).

Table 2. Number of subjects in three studies, according to use and type of laxative

Use of laxative (≥once per week)	Study					
	Los Angeles		North Carolina-1 ^a		North Carolina-2 ^b	
	Cases	Controls	Cases	Controls	Cases	Controls
No	401	412	206	350	123	145
Yes						
Phenolphthalein-containing	9	4	9	18	4	3
Other type	78	72	21	41	15	21

^aIn the North Carolina-1 study (1988–1990), phenolphthalein-containing laxatives were used occasionally by 82 subjects, once per month by 28 subjects, once a week by 21 subjects, and once a day or more by 6 subjects.

^bIn the North Carolina-2 study (1992–1995), phenolphthalein-containing laxatives were used occasionally by 27 subjects, once per month by 13 subjects, once a week by 6 subjects, and once a day or more by 1 subject.

Table 3. Multivariate-adjusted odds ratios (95% confidence intervals) for adenomatous colorectal polyps associated with laxative use in three studies, according to use and type of laxative

Use of laxative (≥once per week)	Study		
	Los Angeles ^a	North Carolina-1 ^b	North Carolina-2 ^c
No	1	1	1
Yes			
Phenolphthalein-containing	1.8 (0.5–6.2)	1.0 (0.4–2.2)	1.1 (0.2–5.7)
Other type	1.3 (0.9–1.9)	1.0 (0.5–1.7)	0.9 (0.4–1.8)

^aThe adjustment factors used were alcohol, smoking, vigorous activity, and intake of energy, saturated fat, and fruits and vegetables.

^bThe adjustment factors used were age, sex, alcohol, smoking, leisure activity, and intake of energy, total fat, and fiber from fruits and vegetables for North Carolina-1 (1988–1990).

^cThe adjustment factors used were age, sex, alcohol, smoking, hard physical activity, and intake of energy, total fat, and fiber from fruits and vegetables for North Carolina-2 (1992–1995).

times/week, was 1.2 (CI, 0.8–1.8). When the results for laxatives shown in Table 3 were additionally adjusted for frequency of bowel movement, the odds ratios were unchanged. In North Carolina, constipation was not related to risk of polyps in either study. The odds ratio for adenomas among subjects having a bowel movement more than 7 times/week, as compared to less than 7 times/week, was 1.0 in North Carolina-1 and 1.2 (CI, 0.8–1.8) in North Carolina-2. For the North Carolina phenolphthalein results shown in Table 3, additional adjustment for constipation or bowel movement did not materially alter the findings.

Discussion

In the populations studied, few subjects reported using phenolphthalein-containing laxatives with any appreciable frequency; thus, the estimates of association in the data are imprecise. In the North Carolina studies, an association of phenolphthalein-containing laxative use with risk of colorectal adenomas was not found. In the Los Angeles study, the odds ratio of 1.8 associated with use once a week or more was suggestive of an association, but the confidence interval was wide. Although the Los Angeles data also showed an increase in risk with number of times a phenolphthalein-

containing laxative was used per week, an association with years of use or number of times taken was not observed. Overall, these data suggest use of phenolphthalein-containing laxatives does not increase risk of adenomatous colorectal polyps.

Mechanistic studies suggest that phenolphthalein is clastogenic and estrogenic; this had led to its testing by the National Toxicology Program (13). Phenolphthalein-induced tumors were observed in rats (pheochromocytoma, renal adenoma and carcinoma) and in mice (histiocytic sarcoma, lymphoma, and ovarian stromal cell tumor). The type of cancer caused by an agent in animal models, however, does not always predict the affected site in humans (14). The effects caused by phenolphthalein in the National Toxicology Program studies suggested that the mechanism of action was by both estrogenic and other pathways (1). Recent epidemiologic evidence shows that use of hormone replacement therapy reduces risk of colorectal neoplasms (15). Thus, the possibility exists that an adverse effect of phenolphthalein on colorectal adenomas was balanced by a protective estrogenic action.

Kune (16) examined the association of colorectal cancer with any use of phenolphthalein-containing laxatives and found the odds ratio to be 1.35 (not significant). In the same study, the odds ratio associated with any use of laxatives of any type was 1.0. In a meta-analysis of 14 case-control studies of cathartic use and risk of colorectal cancer, the odds ratio associated with use of cathartics was 1.46 (CI, 1.33–1.61) (2). This summary was based on study-specific estimates that were not adjusted for constipation, and constipation was also associated with risk. Jacobs and White (17) recently reported an association of laxative use and risk of colorectal cancer, with an odds ratio of 2.8 (CI, 1.0–4.6) for 350 or more lifetime uses compared with no regular use. This association, however, disappeared when adjusted for frequency of constipation. Thus, the evidence that laxative use is an independent risk factor for colorectal cancer appears weak. The present data further suggest no evidence of an association of recent laxative use with risk of adenomatous polyps.

Because data implicating phenolphthalein as a carcinogen were not available at the start of these studies, the questions used to ascertain laxative use were not focused on use of phenolphthalein-containing laxatives, nor were they especially detailed in the history of use obtained. Use of phenolphthalein-containing laxatives was undoubtedly underestimated, and past use was not specifically addressed. Misclassification of exposure caused true associations, if any, to be underestimated. The accuracy of the exposure measure can be further questioned because the condition precipitating the endoscopy, if there was one, might have affected laxative use. Finally, the rate of participation was sufficiently low in the second North Carolina study as to raise the possibility of bias due to nonresponse; however, the decision to participate was made before the subjects knew if they had adenomatous polyps, and both North Carolina studies gave the same result. Potential shortcomings notwithstanding, other results from the three studies have been consistent with the general literature on risk factors for colorectal polyps (7,8).

In summary, data from three studies do not support the hypothesis that laxatives in general or phenolphthalein in particular are associated with presumed colon cancer precursors. Because the risk factors for cancer and adenomas do not always appear to be the same (18) and because the studies analyzed here were not designed to test the laxative hypothesis, a definitive statement on the role of phenolphthalein in the etiology of colorectal neoplasia would be premature.

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