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Exposure to phthalate-containing prescription drugs and the risk of colorectal adenocarcinoma: A Danish nationwide case-control study

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Abstract

Purpose: Some drug products contain phthalates as excipients, and in vitro studies have demonstrated that phthalates interfere with cellular mechanisms involved in colorectal cancer development. We therefore examined the association between cumulative phthalate exposure from drug products and risk of colorectal adenocarcinomas.

Methods: We used the Danish Cancer Registry to identify all patients with incident colorectal adenocarcinoma from 2008 to 2015 (n = 25 814). Each cancer case was matched to ten population controls. Linking information from Danish registers, we quantified cumulative phthalate exposure to the ortho-phthalates diethyl phthalate (DEP) and dibutyl phthalate (DBP) as well as enteric phthalate polymers from orally administered drugs. The association between cumulative phthalate exposure and colorectal cancer was estimated using conditional logistic regression.

Results: Cumulative exposure to ortho-phthalates exceeding 500 mg was associated with lower odds of colorectal cancer diagnosis (OR_{adj} = 0.89; 95% CI, 0.81-0.96). Similar associations were observed for all DEP exposure exceeding 500 mg. Subgroup analysis excluding NSAID users, demonstrated that ortho-phthalate exposure was positively associated with colorectal cancer (OR_{adj} = 1.26; 95% CI, 1.05-1.51).

Conclusion: We found an apparent overall protective effect of cumulative phthalate exposure from drug excipients for colorectal adenocarcinoma. Omitting NSAID users reversed the signal and suggested a slightly increased risk associated with high cumulative ortho-phthalate exposure.

KEYWORDS

colorectal neoplasms, Denmark, dibutyl phthalate, diethyl phthalate, excipients, pharmacoepidemiology

1 | INTRODUCTION

The widespread use of phthalates as softeners in plastic products has gained increasing attention since phthalates are suspected endocrine disruptors and reproductive toxins.[1] Although the carcinogenic properties of phthalates are still uncharacterized, some epidemiologic studies have associated ortho-phthalate exposure with incident breast cancer in humans.[2,3]

Ortho-phthalates are known to stimulate the epithelial-to-mesenchymal transition necessary for cancer invasion and metastasis, mediated by histone deacetylase 6.[4] In vitro studies support a role of phthalates in mechanisms of colon carcinogenesis. Additionally, a dose-dependent effect of ortho-phthalates on aryl hydrocarbon receptor (AhR) function has been suggested. The AhR is a transcription factor that plays an important role in cell proliferation and differentiation and in tumor development.[5]

Some phthalates are used as excipients in pharmaceuticals. Their water resistant and acid stable properties are utilized in the pharmaceutical production of sustained or delayed release preparations.[6] Among users of phthalate-containing drugs, an up to 50-fold increased urinary concentration of phthalate metabolites was demonstrated compared with nonusers.[7] The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) are aware of the potential harmful phthalate exposure from pharmaceutical preparations, and both agencies have published guidelines on limiting pharmaceutical phthalate exposure from orally administered drug products.[8,9] Recent population-based Danish data suggest that exposure to phthalates from drugs is not negligible, with a median dibutyl phthalate (DBP) exposure from prescription drugs that remained above European regulatory limit of exposure.[10,11]

This led us to consider if the phthalate exposure from orally administered drugs carries an excess risk of developing colorectal adenocarcinomas. We therefore performed a Danish nationwide registry-based case-control study to examine the association between cumulative pharmaceutical phthalate exposure and risk of colorectal adenocarcinoma.

KEY POINTS

- Some prescription drugs contain phthalates.
- Exposure may be significant.
- Little is known about the carcinogenic properties of phthalates.
- Omitting NSAID use, major exposure to phthalates was associated with a slightly increased risk of colorectal adenocarcinoma.
- Findings are unlikely of clinical relevance.

2 | METHODS AND MATERIALS

The study was conducted according to STROBE guidelines for reporting observational studies,[12] using a nationwide case-control approach investigating the cumulative phthalate exposure from orally administered drug products among individuals diagnosed with colorectal cancer (cases) and population-based cancer-free persons (controls).

2.1 | Data sources

Virtually all medical care in Denmark is furnished by the national health authorities, allowing true population-based register linkage studies covering all inhabitants of Denmark. A variety of information is captured in the Danish registries.[13] Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968.[14] We used information from five Danish nationwide registries: the Danish Cancer Registry,[15] the National Prescription Registry,[16] the National Patient Register,[17] Registers in Statistics Denmark on educational level,[18] and the Civil Registration System.[13]

Detailed information on data sources is presented in Appendix S1A, and codes for cancer diagnoses, drug exposures, and covariates are available in Appendix S1B.

By linking data from an internal database maintained by the Danish Medicines Agency with the National Prescription Registry, we could quantify phthalate exposure on the level of the individual. The internal Danish Medicines Agency database provided detailed information on phthalate content per tablet or capsule, in specific marketed drug products. This database records information on type and amount of all excipients in drugs with Danish marketing permission from 2004 onwards. All changes in quantitative compositions of excipients are recorded. Each specific drug product can be identified by the Nordic product code (VNR), and drugs are classified according to the Anatomic Therapeutic Chemical (ATC) index, developed by the World Health Organization. Only orally administered drugs were included.

2.2 | Sampling of cases and controls

From the Danish Cancer Registry, we identified all patients (cases) in Denmark with a first-time diagnosis of colorectal cancer (ICD10: C18-20) in the period 2008 to 2015. The case population was restricted to individuals with histologically verified adenocarcinoma. The date of the cancer diagnosis was used as the index date. Exclusion criteria were age outside the range 18 to 85 years at index date and any residency outside Denmark within 10 years prior to index date. We further excluded cases with a history of other cancers (except nonmelanoma skin cancer) as well as individuals with disorders associated with an increased risk of colorectal cancer: hereditary nonpolyposis colon cancer, familial adenomatous polyposis, and inflammatory bowel disease (IBD), defined either through a diagnosis or use of anti-inflammatory drugs specific to IBD, ATC-group A07E. Lastly, patients with total colectomy were excluded.

Controls were selected using risk set sampling, applying the same exclusion criteria as for cases. For each case, we selected 10 cancer-free controls among all Danish residents of the same gender and birth year. Controls were identified through the civil registration system covering all Danish inhabitants,[13] and they were assigned an index date identical to that of the corresponding case. Subjects were eligible for being sampled as controls before they became cases.

2.3 | Exposure definition

Exposure to ortho-phthalates or enteric phthalate polymers was quantified by cumulative exposure during the period 2004 to 2015. We did this by linking information on pack size and phthalate amount per pill or tablet for all dispensed prescriptions by all subjects included in our studies. Ever-exposed designates those who had greater than or equal to one phthalate-containing product dispensed.

Exposure was also characterized by specific phthalate: ortho-phthalates by diethyl phthalate (DEP) and DBP and the individual enteric phthalate polymers cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), and polyvinyl acetate phthalate (PVAP). Exposure categories were somewhat arbitrarily. We aimed to separate the risk among those exposed to low amounts of phthalates from those exposed to larger amounts and still provide sufficient number of subjects within each category to produce meaningful estimates.

High exposure to any ortho-phthalate was defined as greater than 500 mg of cumulative phthalate exposure, intermediate exposure was defined as 250 to 499 mg of cumulative exposure, and low exposure was defined as less than 250 mg of cumulative exposure over the study period. For enteric phthalate polymers, the corresponding categories were greater than 10 000, 5000 to 9999, and less than 4999 mg of cumulative exposure. Never-exposed groups were defined for ortho-phthalates and enteric phthalate polymers.

2.4 | Confounding variables

The following potential confounders were identified and incorporated as dichotomic variables in the analyses: (a) Use of drugs known or suspected to modify the risk of colorectal adenocarcinoma including use of statins, antidepressants, and hormone replacement therapy; (b) prior diagnoses of diabetes, chronic obstructive pulmonary disease (COPD), and alcohol-related disease; and (c) highest achieved education (as a crude measure of socioeconomic status). Dichotomization was determined by classifying patients who redeemed at least one of the prescription drugs or receiving at least one of the ICD-10 codes during the study period as being exposed or diagnosed. Use of low-dose aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) were incorporated as categorical variables in the analyses based on number of redeemed prescriptions. Low-dose ASA was categorized in zero, one to 15, or greater than 15 redeemed prescriptions, and NSAIDs were categorized in zero, one to five and greater than five redeemed prescriptions. As in the assessment of drug exposure, we disregarded the period 1 year prior to the index date in the identification of confounder status (ICD-10 codes and ATC-codes are listed in Appendix S1B).

2.5 | Main analysis

The analysis followed a conventional matched case-control approach. We tabulated the frequency and proportion of cases and controls within categories of the exposures and covariates. We used conditional logistic regression to estimate ORs for colorectal adenocarcinoma associated with high exposure to any ortho-phthalate, DEP, and DBP or to any enteric phthalate polymer, adjusting for potential confounders. We performed dose-response analyses using above-mentioned predefined exposure groups. In all analyses, exposure to any phthalate was compared with never-exposure (reference category). In all exposure calculations, we disregarded prescriptions redeemed within 1 year prior to the index date. This was done to reduce the possibility of reverse causation, while also judging that such recent exposure is unlikely to affect cancer development.[19]

2.6 | Preplanned sensitivity and subanalyses

We examined heterogeneity of phthalate/colorectal adenocarcinoma associations within strata of gender, age, year of sampling, stage of disease, topography, and no history of diabetes or alcohol abuse. Further, we performed an analysis excluding lithium-treated patients and patients treated with NSAIDs or low-dose ASA to see if extensive representation of these specific drugs influenced our results. This was done because DBP exposure is mainly driven by lithium products[11] and as long-term exposure to NSAIDs and low-dose ASA is known to reduce the risk of colorectal cancers.[20]

2.7 | Other

The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board.[21]

3 | RESULTS

We identified 25 814 colorectal cancer cases with histologically verified colorectal adenocarcinoma eligible for inclusion (Figure 1). To these cases were matched 258 140 cancer-free population controls. Most of the included cases and controls were above 70 years of age (51%), and 56 % were men. For ortho-phthalate exposure, drug use, comorbidities, and educational level, the cases and controls were balanced. Baseline characteristics of cases and controls are shown in Table 1.

Overall, 6607 (25.6%) of cases had used phthalate-containing orally administered drugs compared with 68 600 (26.6%) of controls. Among these, 674 cases (2.6%) and 7724 controls (2.9%) were classified as having high exposure to ortho-phthalates. This yielded an adjusted OR of 0.89 (95% CI, 0.81-0.96) for the association between high ortho-phthalate exposure and the risk of colorectal adenocarcinoma (Table 2).

Dose-dependent effect was not seen across exposure levels among those exposed to any ortho-phthalate ($P = 0.63$, test for trend). There were no apparent associations for exposure below 500 mg. Analyses of specific phthalate exposures consistently returned estimates below the null across levels of DEP and DBP with cumulated exposure exceeding 250 mg (Table 2). Likewise, inverse associations were seen in analyses stratified by age, gender, cancer location, and stage of disease.

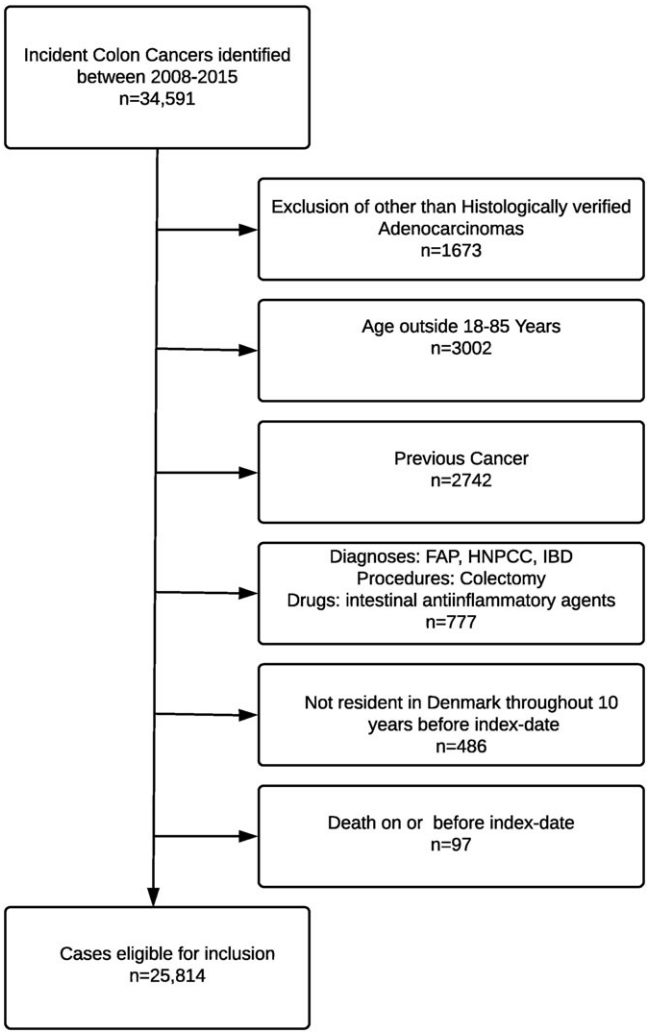

FIGURE 1 Flowchart displaying selection of cases

TABLE 1 Characteristics of cases and their matched controls

	Cases	Controls
All	(n = 25 814)	(n = 258 140)
Male gender	14 518 (56.2%)	145 180 (56.2%)
Age		
Median (IQR, y)	70 (63-76)	70 (63-76)
<50 y	1111 (4.3%)	11 110 (4.3%)
50-69 y	11 485 (44.5%)	114 850 (44.5%)
70+ y	13 218 (51.2%)	132 180 (51.2%)
Cancer location		
Colon, proximal	7442 (28.8%)	-
Colon, distal	8197 (31.8%)	-
Colon, unknown	9170 (35.5%)	-
Rectum	1005 (3.9%)	-
Ortho-phthalate exposure		
Never exposed	19 207 (74.4%)	189 540 (73.4%)
0-249 mg	5511 (21.3%)	56 152 (21.8%)
250-499 mg	422 (1.6%)	4724 (1.8%)
≥500 mg	674 (2.6%)	7724 (3.0%)
Drug use		
Low-dose aspirin	6835 (26.5%)	69 110 (26.8%)
Nonaspirin NSAID	14 850 (57.5%)	152 492 (59.1%)
Statins	8130 (31.5%)	79 582 (30.8%)
Estrogens	4362 (16.9%)	47 171 (18.3%)
Antidepressants	4300 (16.7%)	48 615 (18.8%)
Comorbidities		
Diabetes	2354 (9.1%)	20 762 (8.0%)
COPD	1577 (6.1%)	14 371 (5.6%)
Alcohol-related diseases	1325 (5.1%)	11 913 (4.6%)
Education		
Short (7-10 y)	9679 (37.5%)	95 104 (36.8%)
Medium (11-13 y)	10 383 (40.2%)	98 284 (38.1%)
Long (>13 y)	4959 (19.2%)	53 232 (20.6%)
Unknown	793 (3.1%)	11 520 (4.5%)

Abbreviations: IQR: inter quartile range; NSAID's: nonsteroidal anti-inflammatory drugs.

Excluding patients diagnosed with diabetes, patients treated with lithium, patients treated with ASA products, and patients treated for alcohol abuse did not alter our findings (Table 3). However, excluding patients with either greater than one or greater than three redeemed NSAID prescriptions returned estimates suggesting an increased colorectal cancer risk with phthalate exposure, with ORs of 1.26 (95% CI, 1.05-1.51) and 1.21 (95% CI, 1.04-1.41), respectively (Table 3). Analysis of a possible interaction between NSAID use and phthalate ever-exposure yielded an OR of 0.92 (95% CI, 0.86-0.99), suggesting weak effect modification, whereby the OR for the phthalates/cancer association is slightly lower in the presence of concurrent NSAID therapy.

Results for ortho-phthalate containing drugs used by study population and exposure to any enteric phthalate polymer as well as exposure to the individual compounds CAP, HPMCP, and PVAP are presented in Supporting Information. The following findings were seen among those exposed to any enteric phthalate polymer; cumulative exposure between 0 and 4999 mg yielded an adjusted OR of 0.94 (95% CI, 0.91-0.98), cumulative exposure between 5000 and 9999 mg yielded an adjusted OR of 1.00 (95% CI, 0.89-1.12) and greater than or equal to 10 000 mg resulted in an adjusted OR 1.11 (95% CI, 1.03-1.19). An equivalent pattern of was seen for HPMCP, but not for CAP and PVAP (Table S1).

Changing the lag time to either 6 months or 2 years had no effect on our estimates when compared with 1-year lag (data not shown).

4 | DISCUSSION

In this study, Danish users of phthalate-containing drug products with cumulated exposure to any ortho-phthalate exceeding 500 mg across the study period appeared less likely to develop colorectal adenocarcinomas compared with nonusers, with an adjusted OR of 0.89 (95% CI, 0.81-0.96). Consistency in inverse effect of DEP and DBP exposure was observed across all exposure levels exceeding 250 mg. Post hoc

TABLE 2 Exposure status and cumulated exposure to any ortho-phthalate during 2004-2015[a]

	Cases	Controls	Crude OR	Adjusted OR[b]
Ortho-phthalates exposure status				
Never exposed	19 207	189 540	1.0 (ref.)	1.0 (ref.)
Ever exposed	6607	68 600	0.95 (0.92-0.98)	0.98 (0.95-1.01)
Ever exposure to ortho-phthalates				
0-249 mg	5511	56 152	0.97 (0.94-1.00)	1.00 (0.96-1.03)
250-499 mg	422	4724	0.88 (0.79-0.97)	0.91 (0.82-1.01)
≥500 mg	674	7724	0.86 (0.79-0.93)	0.89 (0.81-0.96)
DEP				
0-249 mg	5312	54 082	0.97 (0.94-1.00)	1.00 (0.96-1.03)
250-499 mg	402	4545	0.87 (0.78-0.96)	0.90 (0.81-1.00)
≥500 mg	568	6541	0.86 (0.78-0.94)	0.88 (0.80-0.96)
DBP				
0-249 mg	394	4124	0.96 (0.86-1.07)	1.00 (0.90-1.11)
250-499 mg	22	283	0.81 (0.52-1.26)	0.84 (0.54-1.30)
≥500 mg	114	1253	0.90 (0.74-1.10)	0.95 (0.78-1.16)

[a]Ortho-phthalate exposure is specified to either diethyl phthalate (DEP) or dibutyl phthalate (DBP) exposure.

[b]Fully adjusted model included following drugs and diagnoses: statins, antidepressants, hormone replacement therapy, NSAIDs, ASA, diabetes, chronic obstructive pulmonary disease, and alcohol-related disease, highest achieved education.

analysis excluding NSAID users led to a reversal of the association, indicating a positive association between phthalate exposure and colorectal cancer risk.

Use of high-quality registries covering the entire Danish population is the main strength of our study. In addition, primary nonadherence was eliminated by the use of dispensed prescriptions.[22] Additionally, the influence of secondary nonadherence was reduced, because exposure was quantified in cumulative amount. Patients missing doses of their medications often stretch the coverage of their prescription. In this way, these patients are exposed to the entire amount of phthalates from the dispensed product.[23] The principle weakness of this study is lack of information on lifestyle factors known to influence the risk of colorectal adenocarcinomas such as smoking,[24] alcohol consumption,[25] body weight,[26] and certain diets.[24] While we controlled for a number of possible confounders and covariates, we cannot exclude confounding by indication. The distribution of quantitative phthalate exposure by drug is listed in Tables S2 and S3. Quantitatively, the most important contributions to the cumulative ortho-phthalate exposure were from preparations containing lithium, multienzymes, theophylline, erythromycin, and diclofenac (Tables S2 and S3).

Our primary finding was in direct opposition to our hypothesis as data suggested a protective effect rather than representing a risk factor. Estrogenic activity of ortho-phthalates could be a plausible biological explanation supporting a protective effect of phthalates towards colorectal cancer. Subgroup analysis omitting NSAID exposed individuals eliminated the protective association and even suggested a slightly increased risk from high cumulative ortho-phthalate exposure. As this finding emerges from a post hoc analysis, interpretation of this result should be made with caution. We believe the most plausible explanation for our primary result is substantial confounding from NSAID use. NSAID exposure is known to reduce the risk of colorectal cancers,[20] which could explain the protective effect observed. Ibuprofen, diclofenac, naproxen, and ketoprofen were available as phthalate-containing variants throughout the study period, and NSAID products represented 14.9% of DEP exposure and 0.9% of DBP exposure (Tables S2 and S3). No phthalate-containing aspirin products were available. The quantitatively most important contribution to DBP exposure was from preparations with lithium. About 50% of lithium reimbursed in the study period contained ortho-phthalate,[10,11] but neither depression nor lithium itself appear associated with increased risk of colorectal cancer.[27,28]

Based on the currently available data, the US Consumer Product Safety Commission have not classified DEP and DBP as carcinogenic compounds.[29,30] Only a few epidemiological studies on the carcinogenic effect of phthalates in humans exist. Lopez et al demonstrated elevated risk of breast cancer among Mexican women with high urinary concentrations of monoethyl phthalate (MEP), a DEP metabolite. The study compared the lowest tertile of exposure to the highest tertile, and an OR of 2.20 (95% CI, 1.60-10.70) for the risk of breast cancer was found.[2] Holmes et al conducted a case-control study in Alaska Native women, investigating the association between breast cancer and exposure to several environmental chemicals. The authors did not demonstrate an increased risk of breast cancer among women high urinary concentrations of MEP or monobutyl phthalate (MBP), a DBP metabolite. Urinary concentrations above the geometric mean yielded adjusted ORs of 0.55 (95% CI, 0.26-1.18) and 0.66 (95% CI, 0.32-1.39) for MEP and MBP, respectively.[3] Occupational exposure to diethylhexyl phthalate-containing polyvinyl chloride (PVC) and the risk of testicular cancer were investigated in a study by Hardell et al. Overall, a harmful association between occupational PVC exposure and the risk of seminomas with an OR at 5.6 (95% CI, 1.1-196) was demonstrated.[31] However, this study covered multiple potential harmful chemical exposures, including diethylhexyl phthalate, which is not used as excipient in orally administered drugs, in consequence of PVC exposure.

Unlike our study, the study by Hardell et al investigated occupational or environmental exposures with no quantitative control of actual exposures on the level of the individual. The studies all had small sample sizes, and they were investigating the risk of cancers connected to endocrine disrupting properties of phthalates using biomonitoring and/or questionnaire data.

We had information on exposure from 2004 until 1 year prior to the index date or date of receiving cancer diagnosis. We included up to 11 years of exposure during the period 2004 to 2015. During this period, only 2.6% of cases and 3.0% of controls in this study were exposed to more than 500 mg of ortho-phthalate from prescription drugs. Compared with environmental exposure, the cumulated exposure from prescription drugs during the study period is of modest magnitude in most of the subjects included in this study. However, some users of phthalate-containing drug products are highly exposed, and their exposure might be markedly higher than exposure from environmental sources.[11] The estimate of minimum environmental exposure to DEP and DBP exceeds 1200 mg throughout the study

TABLE 3 Stratified analyses by age, sex, cancer localization, and stage of disease[a]

	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude OR	Adjusted OR[b]
All	674/19 207	7724/189 540	0.86 (0.79-0.93)	0.89 (0.81-0.96)
Age				
<50 y	10/872	141/8341	0.69 (0.36-1.32)	0.68 (0.35-1.31)
50-69 y	242/8651	2761/85 238	0.86 (0.75-0.98)	0.87 (0.76-1.00)
70+ y	422/9684	4822/95 961	0.87 (0.78-0.96)	0.90 (0.81-1.01)
Sex				
Male	334/11 083	3787/109 983	0.88 (0.79-0.99)	0.89 (0.79-1.00)
Female	340/8124	3937/79 557	0.84 (0.75-0.94)	0.89 (0.79-1.00)
Localization				
Proximal	236/5377	2400/54 110	0.98 (0.86-1.13)	0.98 (0.85-1.13)
Distal	206/6122	2408/60 178	0.84 (0.73-0.98)	0.87 (0.75-1.01)
Rectum	202/6971	2575/67 907	0.77 (0.66-0.89)	0.81 (0.70-0.94)
Unknown	30/737	341/7345	0.83 (0.56-1.23)	0.82 (0.55-1.23)
Stage of disease				
Localized	240/6649	2781/66 597	0.86 (0.75-0.99)	0.84 (0.73-0.96)
Nonlocalized	304/9170	3554/89 739	0.84 (0.74-0.94)	0.91 (0.81-1.03)
Unknown	130/3388	1389/33 204	0.92 (0.76-1.11)	0.92 (0.76-1.11)
Other subgroups				
Excluding lithium exposed	581/19 185	6856/189 327	0.83 (0.76-0.91)	0.85 (0.78-0.93)
Excluding diabetics	561/17 665	6537/176 156	0.85 (0.78-0.94)	0.89 (0.82-0.98)
Excluding alcohol abusers	605/18 337	6885/182 072	0.87 (0.80-0.95)	0.91 (0.83-0.99)
Excluding NSAID exposed (≥1 prescription)	173/9583	1439/92 782	1.26 (1.05-1.50)	1.26 (1.05-1.51)
Excluding NSAID exposed (≥3 prescriptions)	228/11 861	1939/114 644	1.20 (1.04-1.40)	1.21 (1.04-1.41)
Excluding ASA exposed	419/14 536	4529/142 885	0.91 (0.82-1.01)	0.93 (0.84-1.04)
Excluding NSAID & ASA users (≥1 prescription)	477/16 559	5073/162 174	0.92 (0.83-1.01)	0.94 (0.85-1.04)
Restricting to NSAID users	501/9624	6285/96 758	0.81 (0.73-0.90)	0.83 (0.75-0.92)
Restricting to ASA users	255/4671	3195/46 655	0.77 (0.66-0.90)	0.80 (0.68-0.94)
Restricting to diabetics	113/1542	1187/13 384	0.75 (0.52-1.09)	0.80 (0.55-1.17)
Restricting to alcohol abusers	69/870	839/7468	0.78 (0.43-1.42)	0.93 (0.49-1.77)
Restricting to lithium users	581/19 185	6856/189 327	0.83 (0.76-0.91)	0.85 (0.78-0.93)
Restricting to those sampled 2004-2009	162/4409	1771/43 615	0.88 (0.75-1.04)	0.90 (0.76-1.06)
Restricting to those sampled 2010-2015	512/14 798	5953/145 925	0.85 (0.78-0.94)	0.88 (0.80-0.97)

[a]Subgroup analyses excluding or restricting to certain populations.

[b]Fully adjusted model included following drugs and diagnoses: statins, antidepressants, hormone replacement therapy, NSAIDs, ASA, diabetes, chronic obstructive pulmonary disease, and alcohol-related disease, highest achieved education.

period. This is based on estimates of human environmental DEP-exposure between 0.0023 and 0.012 mg/kg/day or about 696 mg throughout the study period for a 70-kg person.[32-34] Likewise, DBP-exposure estimates are 0.001 to 0.005 mg/kg/day, or a minimum exposure about 528 mg throughout the study period for a 70-kg person.[35,36] Additionally, information on a specific source of exposure for up to 11 years is rather limited, considering that most humans are exposed to phthalates from environmental sources, throughout their entire lifetime.

5 | CONCLUSION

An apparent overall slightly protective effect of cumulative phthalate exposure from drug excipients for colorectal adenocarcinoma was demonstrated. Omitting NSAID users from the analysis reversed the signal and suggested a slightly increased risk associated with high cumulative exposure to ortho-phthalates. Regardless of assumptions on causality, the signals are weak and unlikely to be of meaningful clinical relevance.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTIONS

P. D. and T. P. A. were responsible for the initial concept. Z. N. E., A. P., and P. D. A. were responsible for compiling data. All authors contributed to the interpretation of the data and results. Primarily, the manuscript was drafted by Z. N. E. and secondly revised carefully for important intellectual content and approved by all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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