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# Association of smoking with neutropenia and diarrhea in patients receiving irinotecan: A retrospective cohort study

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## ABSTRACT

**Aim**: To evaluate the association between smoking status and irinotecan-related neutropenia and diarrhea, while exploring the potential impact of smoking intensity on these clinical outcomes.

**Method:** We conducted a retrospective cohort study of 58 patients receiving irinotecan-based chemotherapy, classified as active smokers (n=21) or non-smokers (n=37). The incidence and severity of neutropenia and diarrhea, along with granulocyte-colony stimulating factor (G-CSF) use, loperamide requirements, and treatment discontinuation rates, were compared between groups. An exploratory subgroup analysis was performed to assess the relationship between daily cigarette consumption and toxicity grades.

**Results:** In the primary analysis, no significant differences were found between smokers and non-smokers regarding neutropenia (p=0.430), diarrhea (p=0.921), G-CSF use (p=0.198), loperamide use (p=0.562), or treatment discontinuation (p=0.602). However, exploratory stratification by smoking quantity revealed a significant association with neutropenia patterns (p=0.014); higher cigarette consumption was correlated with a lower incidence of moderate-to-severe neutropenia. No significant correlation was observed between smoking quantity and diarrhea or other clinical endpoints.

**Conclusion:** While smoking status alone did not significantly affect irinotecan-related toxicities in this cohort, our findings suggest a dose-dependent relationship between smoking intensity and neutropenia. These results potentially reflect altered systemic exposure to the active metabolite SN-38. Given the retrospective nature and small subgroup sizes, these findings are hypothesis-generating and warrant validation in larger prospective trials incorporating pharmacokinetic and genetic data.

**Keywords:** Smoking, irinotecan, cancer, neutropenia.

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## Introduction

Irinotecan, a camptothecin derivative, is widely used in the treatment of various solid tumors, including colorectal, gastric, pancreatic, and lung cancers [1]. However, its clinical utility is frequently hampered by severe, dose-limiting toxicities—specifically neutropenia and delayed-onset diarrhea. These adverse events often necessitate dose reduction, treatment delays, or discontinuation, thereby compromising therapeutic efficacy and patient outcomes [1, 2].

Irinotecan is a prodrug that undergoes enzymatic conversion to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38),

primarily by hepatic carboxylesterases and plasma butyrylcholinesterase [3]. SN-38 exhibits markedly greater cytotoxic activity—approximately 100- to 1000-fold higher—than the parent compound, and its systemic exposure demonstrates substantial interindividual variability [4].

The active metabolite SN-38 is predominantly inactivated through glucuronidation mediated by uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes, mainly UGT1A1 and UGT1A9 [5]. Additional non-hepatic UGT isoenzymes also contribute to the conversion of SN-38 to its glucuronide form, which is subsequently excreted into bile [6]. This glucuronidation process markedly increases the polarity of SN-38, facilitating its elimination from the body [7]. In parallel, irinotecan itself is metabolized by cytochrome P450 enzymes, particularly CYP3A4 and CYP3A5, resulting in less pharmacologically active metabolites [8]. The gut microbiota may further influence irinotecan metabolism through bacterial β-glucuronidase activity, which can reconvert SN-38 glucuronide back to its active form in the intestinal lumen [9].

The pharmacokinetics of irinotecan are highly variable and may be influenced by multiple factors, including age, sex, dose intensity, timing of administration, hepatic function, and concomitant medications [1, 10]. Irinotecan is particularly susceptible to drug–drug interactions, and several medication classes—such as anticonvulsants, antidepressants, antiretrovirals, and nonsteroidal anti-inflammatory drugs—have been shown to alter its pharmacokinetic and pharmacodynamic profile [11-13]. In addition, herbal products, dietary supplements, and lifestyle-related factors have also been reported to interact with irinotecan metabolism [14, 15].

Cancer remains a leading cause of mortality worldwide, accounting for a substantial proportion of deaths in individuals under 85 years of age [16]. Cigarette smoking is responsible for approximately 30% of all cancer-related deaths [17], and previous studies have reported that 50% to 83% of cancer patients continue to smoke even after diagnosis [18-20]. Continued smoking during cancer treatment has been associated with increased symptom burden, higher risk of second primary malignancies, and poorer survival outcomes [21]. Moreover, smoking has been shown to reduce the effectiveness of chemotherapy, radiotherapy, and immunotherapy, whereas smoking cessation after diagnosis is associated with improved survival [22-24].

The mechanistic link between smoking and altered drug metabolism is primarily driven by polycyclic aromatic hydrocarbons (PAHs) found in cigarette smoke. PAHs are potent inducers of the aryl hydrocarbon receptor (AhR), which subsequently upregulates the expression of cytochrome P450 enzymes (particularly CYP1A1 and CYP1A2) and UGT glucuronosyltransferases [25, 26]. Since UGT1A1 and CYP3A isoforms play key roles in irinotecan metabolism, smoking-induced enzyme induction can accelerate the clearance of both irinotecan and SN-38 [24, 27]. Consequently, this presents a clinical paradox: while rapid clearance might theoretically reduce the incidence of dose-limiting toxicities like neutropenia, it simultaneously risks sub-therapeutic drug exposure and reduced antitumor efficacy. Previous pharmacokinetic studies have supported this, demonstrating that smoking can significantly reduce systemic SN-38 exposure, yet the translation of these pharmacokinetic findings into clinical toxicity patterns remains a critical area of investigation [27].

Given these considerations, the present study aimed to investigate the association between smoking status and the development of neutropenia and diarrhea in patients receiving irinotecan-based chemotherapy. Although pharmacokinetic studies have consistently demonstrated reduced systemic exposure to SN-38 among smokers, the translation of these findings into clinically meaningful toxicity patterns, particularly neutropenia and diarrhea, remains poorly characterized. Specifically, it is unclear whether smoking-related enzyme induction results in measurable differences in real-world treatment-limiting toxicities beyond pharmacokinetic alterations alone. We hypothesized that active cigarette smoking may alter irinotecan metabolism and, consequently, its toxicity profile, potentially leading to differences in neutropenia patterns that could reflect reduced systemic exposure to the active metabolite SN-38.

## Materials and Methods

***Study Design and Participants:*** This retrospective study enrolled 58 cancer patients who received irinotecan at Kütahya Health Sciences University Evliya Çelebi Education and Research Hospital and Kütahya City Hospital between January 2021 and January 2025.

A post hoc power analysis was performed using G*Power (version 3.1) to assess whether the available sample size was sufficient to detect large effect sizes (Cohen's d = 0.8) with 80% power and a two-tailed alpha of 0.05. This analysis indicated that a minimum of 42 participants (21 per group) would be required. The actual sample size of the study (n = 58; 21 smokers and 37 non-smokers) exceeded this threshold, suggesting adequate power to detect large group differences. Given the retrospective design, this analysis was conducted for interpretative purposes only and should not be considered a justification of the study design.
All participants had stage 4 disease, with primary diagnoses of colorectal cancer, gastric cancer, pancreotobiliary cancer, small cell lung cancer, or glioblastoma multiforme.

The patients were categorized into two groups based on their smoking status: active smokers and non-smokers. Smoking status was determined retrospectively based on information available in medical records and patient self-reports at the time of irinotecan initiation. Patients were categorized as smokers if they were actively smoking at the time of irinotecan initiation, and as non-smokers if they had never smoked or had quit smoking more than four weeks prior to treatment. In line with previous studies, patients who had stopped smoking within four weeks before starting irinotecan were excluded from the analysis to avoid potential confounding due to residual hepatic enzyme induction[27]. Objective biomarker confirmation of smoking status was not available due to the retrospective nature of the study.

The smoking group was initially subdivided according to the reported number of cigarettes smoked per day (1–4, 5–14, 15–24, 25–34, 35–44, and ≥45 cigarettes). For statistical analyses, these categories were pragmatically consolidated into four groups (1–14, 15–24, 25–34, and ≥35 cigarettes per day) based on the distribution of smoking intensity within the cohort and the need to maintain sufficient sample size within each subgroup. These smoking quantity categories were not intended to reflect biologically predefined thresholds, but were pragmatically consolidated to align with the distribution of smoking intensity in the cohort and to maintain sufficient subgroup sizes for statistical analysis. Accordingly, analyses

based on smoking quantity were prespecified as exploratory and interpreted with caution.

The smoking and non-smoking groups were broadly similar in baseline characteristics; however, age differed between groups. This observational study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure methodological transparency and completeness[28].

***The inclusion criteria were:***

1. age ≥18 years;
2. regular medical care and follow-up visits;
3. receipt of all treatments at the study hospitals;
4. availability of a complete blood count prior to each treatment.

***The exclusion criteria were:***

1. dose reductions for reasons other than neutropenia or diarrhea;
2. non-compliance with the treatment schedule due to non-medical reasons resulting in treatment delays;
3. presence of other causes of diarrhea;
4. use of drugs, herbal products, or supplements known to significantly affect irinotecan metabolism, including strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin), CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's wort), or herbal preparations with known effects on irinotecan pharmacokinetics (e.g., ginseng, ginkgo biloba);
5. receipt of prophylactic granulocyte-colony stimulating factor (G-CSF).

***Laboratory Assessment:*** Complete blood counts were routinely performed for each patient prior to every treatment. All laboratory tests were conducted at the study hospitals' clinical laboratories. Neutropenia was graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as follows: Grade 0 if the absolute neutrophil count was within the normal range, Grade 1 if the count was between the lower limit of normal and 1,500/mm³, Grade 2 if the count was between 1,000 and 1,500/mm³, Grade 3 if the count was between 500 and 1,000/mm³, and Grade 4 if the count was below 500/mm³. Patients were also categorized based on whether they required granulocyte-colony stimulating factor administration.

***Diarrhea Assessment:*** Patients were assessed for diarrhea at each chemotherapy administration. Diarrhea was assessed and graded according to CTCAE v5.0 as follows: Grade 1 was defined as three additional bowel movements per day, Grade 2 as four to six additional bowel movements per day, and Grade 3 as seven or more additional bowel movements per day. Grade 4 diarrhea was characterized by an increase of more than 10 stools per day over the baseline, the presence of grossly bloody diarrhea, and/or the need for parenteral support. Additionally, patients were categorized based on their requirement for loperamide.

**Chemotherapy Regimens**

The patients were administered one of the following chemotherapeutic protocols: irinotecan as a single agent, the FOLFIRI regimen (comprising 5-fluorouracil, leucovorin, and irinotecan), the FOLFIRINOX regimen (comprising 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan), or irinotecan combined with bevacizumab.

***Data Analysis:*** The statistical analyses were conducted using "IBM SPSS Statistics for Windows, Version 25.0." Descriptive statistics were presented, with categorical variables reported as n and %, and continuous variables

as Mean±SD and Median. Comparisons of categorical variables were performed using Pearson's Chi-Square test and Fisher's Exact test (when expected cell counts were <5). Continuous variables were compared using the Independent Samples t-test or Mann–Whitney U test, depending on the normality of data distribution. Exploratory subgroup analyses were interpreted cautiously given small subgroup sizes and multiple comparisons. Because smokers were younger than non-smokers at baseline, we additionally performed age-adjusted binary logistic regression analyses for the primary toxicity outcomes (grade ≥2 neutropenia and grade ≥2 diarrhea), with smoking status entered as a categorical predictor and age as a continuous covariate. A p-value less than 0.05 was considered statistically significant.

***Ethical Considerations***: This study was conducted with the approval of the Non-Interventional Research Ethics Committee of Bezmialem Vakif University as per the decision number E-54022451-050.04-183062 taken at the meeting held on 05.02.2025 with the number 2025/31. All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

## Results

Sociodemographic and clinical characteristics of the study population according to smoking status are summarized in Table 1. A total of 58 patients were included, with a mean age of 58.47 ± 9.83 years (range, 39–76 years). Most patients were male (70.7%). Twenty-one patients (36.2%) were active smokers, while 37 (63.8%) were non-smokers. Smoking intensity among active smokers ranged from 1 to ≥45 cigarettes per day.

Baseline absolute neutrophil count (ANC) values were comparable between smokers and non-smokers, with median values of 4.5 × $10^9$/L and 4.6 × $10^9$/L, respectively. Apart from age, which differed between groups (smokers were younger), no statistically significant differences were observed between smokers and non-smokers with respect to sex, baseline ANC, primary tumor type, or chemotherapy regimen. The distribution of these baseline characteristics, as well as diarrhea grades, neutropenia grades, loperamide use, granulocyte-colony stimulating factor (G-CSF) administration, and treatment discontinuation due to toxicity, are presented in Table 1.

Comparisons of clinical outcomes according to smoking status are shown in Table 2. No statistically significant differences were observed between smokers and non-smokers with respect to diarrhea (p = 0.921), neutropenia (p = 0.430), loperamide use (p = 0.562), G-CSF administration (p = 0.198), or treatment discontinuation (p = 0.602).

Given the baseline age difference between smokers and non-smokers, age-adjusted binary logistic regression analyses were performed for the primary toxicity outcomes. After adjustment for age, smoking status remained not significantly associated with grade ≥2 neutropenia (OR 1.98, 95% CI 0.56–7.01; p = 0.292) or grade ≥2 diarrhea (OR 0.55, 95% CI 0.15–1.97; p = 0.355).

In an exploratory analysis stratified by smoking quantity, the association between smoking intensity and clinical outcomes is presented in Table 3. A statistically significant association was observed between smoking intensity and the incidence of neutropenia (p = 0.014). However, this was an exploratory analysis with small subgroup sizes (n = 4–9 per group), and five outcomes were tested without correction for multiple comparisons; therefore, this finding should be interpreted cautiously and may not remain significant after conservative adjustment (Bonferroni α = 0.01).

**Table 1.** Sociodemographic and clinical characteristics of the study population by smoking status.

| **Variable** | **Total (n = 58)** | **Smokers (n = 21)** | **Non-smokers (n = 37)** | ***p*** |
|---|---|---|---|---|
| **Age (years)** | | | | **.030[a]** |
| Mean ± SD | 58.47 ± 9.83 | 54.5 ± 8.7 | 60.7 ± 9.9 | |
| **Sex** | | | | .076[b] |
| Male, n (%) | 41 (70.7) | 17 (81.0) | 24 (64.9) | |
| Female, n (%) | 17 (29.3) | 4 (19.0) | 13 (35.1) | |
| **Baseline ANC (×10⁹/L)** | 4.6 ± 1.3 | 4.5 ± 1.2 | 4.6 ± 1.2 | .860[a] |
| **Primary Tumor Site**, n (%) | | | | .846[b] |
| Colorectal | 26 (44.8) | 10 (47.6) | 16 (43.2) | |
| Stomach | 7 (12.1) | 2 (9.5) | 5 (13.5) | |
| Pancreatic adenocarcinoma | 5 (8.6) | 2 (9.5) | 3 (8.1) | |
| Intrahepatic cholangiocarcinoma | 1 (1.7) | 0 (0.0) | 1 (2.7) | |
| Small cell lung cancer | 12 (20.7) | 5 (23.8) | 7 (18.9) | |
| Glioblastoma multiforme (GBM) | 7 (12.1) | 2 (9.5) | 5 (13.5) | |
| **Chemotherapy Protocol**, n (%) | | | | .890[b] |
| Irinotecan | 16 (27.6) | 6 (28.6) | 10 (27.0) | |
| FOLFIRI | 32 (55.2) | 11 (52.4) | 21 (56.8) | |
| FOLFIRINOX | 3 (5.2) | 1 (4.8) | 2 (5.4) | |
| Irinotecan + Bevacizumab | 7 (12.1) | 3 (14.3) | 4 (10.8) | |

*[a] Mann–Whitney U test, [b] Chi-square test or Fisher's exact test, as appropriate. p<.05 statistically significant ANC: absolute neutrophil count; GBM: glioblastoma multiforme; G-CSF: granulocyte-colony stimulating factor.*

**Table 2.** Comparison of various variables with smoking status.

| | Smoking | | |
|---|---|---|---|
| Variables | Yes (N=21) | No (N=37( | *P* |
| Diarrhea, N (%) | | | |
| None | 13 (61.9) | 19 (51.4) | .921[b] |
| Grade-1 | 3 (14.3) | 6 (16.2) | |
| Grade-2 | 4 (19) | 9 (24.3) | |
| Grade-3 | 1 (4.8) | 3 (8.1) | |
| Neutropenia, N (%) | | | |
| None | 9 (42.9) | 20 (54.1) | .430[b] |
| Grade-1 | 4 (19) | 10 (27) | |
| Grade-2 | 5 (23.8) | 5 (13.5) | |
| Grade-3 and 4 | 3 (14.3) | 2 (5.4) | |
| Loperamide use, N (%) | | | |
| Present | 8 (38.1) | 17 (45.9) | .562[a] |
| Absent | 13 (61.9) | 20 (54.1) | |
| GCSF use, N (%) | | | |
| Present | 5 (23.8) | 15 (40.5) | .198[a] |
| Absent | 16 (76.2) | 22 (59.5) | |
| Treatment Termination, N (%) | | | |
| Present | 2 (9.5) | 3 (8.1) | .602[b] |
| Absent | 19 (90.5) | 34 (91.9) | |

*[a] Pearson Chi Square test, [b] Fisher's Exact test, GCSF: granulocyte-colony stimulating factor, p<.05 statistically significant*

Specifically, higher smoking quantity was associated with a greater proportion of patients without neutropenia and fewer moderate-to-severe neutropenia events across subgroups. No statistically significant associations were found between smoking quantity and diarrhea (p = 0.449), loperamide use (p = 0.317), G-CSFadministration (p = 0.887), or treatment discontinuation (p = 0.486). Given the limited number of patients within individual smoking quantity subgroups, a more granular stratification of neutropenia grades was not feasible.

accounts for approximately 30% of all cancer deaths and 80% of lung cancer deaths[29]. However, research has shown that a substantial portion of cancer patients continue to smoke even after their diagnosis[30]. This may be due to the addictive nature of nicotine, increased stress levels in patients, and a sense of having little left to lose. Furthermore, only 62% of respondents reported being informed about the dangers of smoking by their healthcare providers during cancer treatment[30]. The inadequate patient education provided by clinicians and other healthcare professionals

**Table 3.** Comparison of smoking amounts by various variables.

| | Smoking Amount | | | | |
|---|---|---|---|---|---|
| Variables | 1-15<br>N=9 | 15-24<br>N=4 | 25-34<br>N=4 | 35 ≤<br>N=4 | *P* |
| Diarrhea, N (%) | | | | | |
| None | 4 (44.4) | 2 (50.0) | 3 (75.0) | 4 (100) | .449 |
| Grade-1 | 1 (11.1) | 2 (50.0) | 0 (0.0) | 0 (0.0) | |
| Grade-2 | 3 (33.3) | 0 (0.0) | 1 (25.0) | 0 (0.0) | |
| Grade-3 | 1 (11.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Neutropenia, N (%) | | | | | |
| None | 0 (0.0) | 2 (50.0) | 3 (75.0) | 4 (100) | .014 |
| Grade-1 | 3 (33.3) | 1 (25.0) | 0 (0.0) | 0 (0.0) | |
| Grade-2 | 4 (44.4) | 1 (25.0) | 0 (0.0) | 0 (0.0) | |
| Grade-3 and 4 | 2 (22.2) | 0 (0.0) | 1 (33.3) | 0 (0.0) | |
| Loperamide use, N (%) | | | | | |
| Present | 5 (55.6) | 2 (50.0) | 1 (25.0) | 0 (0.0) | .317 |
| Absent | 4 (44.4) | 2 (50.0) | 3 (75.0) | 4 (100) | |
| GCSF use, N (%) | | | | | |
| Present | 3 (33.3) | 1 (25.0) | 1 (25.0) | 0 (0.0) | .887 |
| Absent | 6 (66.7) | 3 (75.0) | 3 (75.0) | 4 (100) | |
| Treatment Termination, N (%) | | | | | |
| Present | 2 (22.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | .486 |
| Absent | 7 (77,8) | 4 (100) | 4 (100) | 4 (100) | |

*Fisher's exact test was used. Subgroup sizes were small (n = 4–9 per group); therefore, results should be interpreted as exploratory. Five outcomes were tested without adjustment for multiple comparisons (Bonferroni-adjusted α = 0.01). p < 0.05 was considered statistically significant. G-CSF: granulocyte-colony stimulating factor.*

## Discussion

Smoking is a leading preventable contributor to mortality, with estimates indicating that it

may contribute to the persistence of smoking behaviors among cancer patients. Given the

well-established detrimental effects of continued smoking after a cancer diagnosis, healthcare providers should routinely inquire about smoking status during each clinical visit, regardless of whether the cancer type is directly linked to tobacco use. Patients with a history of smoking who are undergoing cancer treatment or post-treatment follow-up should be strongly encouraged to quit, with appropriate psychological and, if necessary, pharmacological support offered to facilitate cessation.

Despite the continued use of irinotecan in oncology, few studies have investigated its association with smoking since the publication of van der Bol et al. This gap may be partly explained by a shift in research priorities toward targeted therapies and immunotherapies, which have dominated clinical trial agendas in recent years. Additionally, it may reflect a declining interest among clinicians in chemotherapy- and smoking-related issues, leading to reduced attention to this intersection in both research and practice. Nevertheless, chemotherapy remains a cornerstone of daily oncology care, and smoking continues to be a prevalent and clinically relevant concern among cancer patients.

Cancer therapies are often administered in combination, containing multiple cytotoxic agents as part of complex treatment regimens. These regimens may also include additional medications to maximize therapeutic benefit, mitigate adverse effects of chemotherapy, or manage concurrent illnesses. Consequently, polypharmacy is highly prevalent in the management of cancer patients[31, 32]. Drug interactions among cancer patients may be more prevalent than commonly assumed, and can often go unnoticed by clinicians[33]. A recent prospective study of ambulatory cancer patients found clinically relevant drug-drug interactions in 27% of cases[34]. Additionally, among cancer patients receiving only supportive care, potential drug interactions were identified in 31% of patients[35]. Irinotecan, one of the drugs most prone to drug interactions, is highly dependent on metabolism for its activity and elimination. Consequently, there is a high likelihood of altered exposure to its key metabolites due to pharmacokinetic drug-drug interactions [36].

Patients with malignant glioma who were concurrently receiving enzyme-inducing antiepileptic drugs exhibited a 3.5-fold higher maximum tolerated dose of irinotecan compared to those not receiving such concomitant medications[37]. When administering irinotecan, the standard dose differs depending on the concomitant use of antiepileptic medications. In routine irinotecan administration, apart from this difference, dose adjustments are not typically made. Consequently, clinicians must exercise caution regarding potential drug interactions.

Not only medications, but also herbal use can interact with irinotecan therapy. For instance, St. John's Wort has been demonstrated to induce CYP3A4 enzyme activity, which may lead to reduced bioavailability and suboptimal treatment of patients receiving irinotecan. Specifically, concomitant administration of St. John's Wort resulted in a 42% decrease in plasma levels of the key active metabolite SN-38 following intravenous administration of irinotecan[15]. Patients should avoid using herbal therapies during irinotecan treatment. If they are insistent on using such products, it is essential that they inform their healthcare provider.

Smoking has been shown to induce the activity of specific cytochrome P450 enzymes that play a crucial role in the metabolism of

numerous medications. The polycyclic aromatic hydrocarbons (PAHs) present in tobacco smoke are primarily responsible for this induction of enzymatic activity. The particular cytochrome P450 isoforms that are potently induced by PAHs include CYP1A1, CYP1A2, and potentially CYP2E1[38].

In the present study, no statistically significant differences in neutropenia, diarrhea, loperamide use, granulocyte-colony stimulating factor administration, or treatment discontinuation were observed between smokers and non-smokers. However, an exploratory analysis revealed that increasing smoking quantity was associated with a lower incidence and severity of neutropenia. This distinction between the primary smoker/non-smoker comparison and the exploratory smoking quantity analysis is important to avoid misinterpretation of the findings.

Because smokers were younger than non-smokers at baseline, we explicitly addressed this imbalance by performing age-adjusted analyses for the primary toxicity outcomes. After adjustment for age, smoking status remained not significantly associated with grade ≥2 neutropenia or grade ≥2 diarrhea, indicating that the absence of significant differences in the primary analyses was not driven by age-related confounding.

Although there were numerical and proportional differences between the groups, the lack of statistical significance in the primary comparison may be attributable to the limited number of smoking patients included in the study (n = 21). This small sample size, particularly within smoking quantity subgroups, substantially limits statistical power and necessitates cautious interpretation of both non-significant and exploratory findings.

When the relationship between smoking amount and these factors was evaluated, it was observed that as the amount of smoking increased, the incidence of neutropenia decreased. However, no statistically significant association was found between the amount of smoking and diarrhea. The literature also indicates that in irinotecan patients who smoke, the incidence of neutropenia decreases, while the frequency of diarrhea remains unchanged [27]. In this case, it can be considered that diarrhea is associated with many other factors in addition to neutropenia. Constipation in cancer patients receiving chemotherapy may develop due to various reasons such as certain medications used, physical inactivity, fluid intake, performance status, and dietary changes. A study found the prevalence of constipation to be 50.3% in cancer patients receiving chemotherapy [39]. These additional contributing factors may have obscured any potential association between smoking and irinotecan-induced diarrhea in our cohort.

The observation that neutropenia differed according to smoking quantity but not smoking status alone suggests that the interaction between smoking and irinotecan metabolism may become more pronounced with increasing tobacco exposure. In our study, a substantial proportion of smokers reported relatively low daily cigarette consumption. Previous literature suggests that consumption of approximately 7–12 cigarettes per day may be sufficient to induce maximal metabolic enzyme activity for certain drugs; however, irinotecan metabolism is considerably more complex. Its efficacy and toxicity are largely determined by systemic exposure to the active metabolite SN-38 [40].

Smoking has been shown to induce UGT1A1 activity, leading to increased glucuronidation of SN-38 and an estimated 40% reduction in systemic SN-38 exposure [27]. This enhanced metabolic clearance provides a plausible mechanistic explanation

for the observed reduction in neutropenia among heavier smokers. Nevertheless, the relationship between smoking intensity and the degree of SN-38 glucuronidation remains incompletely understood and warrants further investigation.

Additionally, in vitro studies have shown that smoking may influence the distribution of irinotecan in red blood cells (RBCs). Although irinotecan generally exhibited relatively high affinity for RBCs, the concentration of irinotecan was higher in the erythrocytes of non-smokers compared to smokers. It has been hypothesized that constituents of tobacco smoke, such as arylamines, directly inhibited the interaction between irinotecan and RBCs [41]. However, these findings are derived from in vitro studies and cannot directly explain the clinical observations of the present study; rather, they should be considered as hypotheses requiring validation in future in vivo investigations.

From a clinical perspective, assessing smoking status before initiating irinotecan treatment is important; however, in real-world practice, achieving smoking cessation within a short period may not always be feasible. Importantly, the observed reduction in neutropenia among heavier smokers may paradoxically reflect lower systemic exposure to SN-38, thereby raising concerns about potentially reduced irinotecan efficacy. Moreover, even if patients quit smoking prior to treatment initiation, smoking-induced physiological and metabolic changes—such as induction of drug-metabolizing enzymes—may persist for weeks or even months and continue to influence irinotecan pharmacokinetics. Therefore, clinicians should be aware that these residual effects may affect treatment outcomes and toxicity profiles despite recent smoking cessation. While it may be tempting to consider dose adjustments for active smokers, there is currently insufficient evidence to support increasing irinotecan doses solely on the basis of smoking status. Instead, careful and individualized monitoring of both efficacy and toxicity is warranted, taking into account patient tolerance, treatment response, and comorbidities. Overall, these findings highlight smoking cessation as a modifiable factor that may optimize both the safety and effectiveness of irinotecan-based chemotherapy.

***Limitations***

This study has several limitations that should be acknowledged. First, the small sample size—particularly within smoking quantity subgroups—limits the statistical power of the analyses and increases the risk of both type I and type II errors. Accordingly, subgroup-based findings (especially those presented in Table 3) should be interpreted as exploratory rather than confirmatory, and the limited number of patients within each subgroup precluded a more granular analysis of neutropenia grades. Second, the categorization of smoking amounts into discrete intervals may have introduced artificial thresholds and reduced sensitivity to detect dose–response relationships. Third, although age-adjusted analyses were performed for the primary toxicity outcomes, potential confounding factors such as treatment regimen and baseline performance status were not adjusted for in the exploratory subgroup comparisons, which may have influenced the observed outcomes.

In addition, the absence of UGT1A1 genotyping data limits insights into interpatient variability in SN-38 metabolism and the risk of hematologic toxicity. Furthermore, although patients taking medications with well-documented interactions with irinotecan were excluded, the study did not systematically record all concomitant drugs, herbal products,

or supplements with potential interaction effects. Smoking status was also determined retrospectively based on medical records and patient self-reports and referred exclusively to conventional cigarette smoking; data regarding alternative nicotine delivery systems, such as e-cigarettes or vape pens, were not systematically available.

Moreover, transfusion data (including packed red blood cell or whole blood transfusions) were not systematically recorded in this retrospective cohort. Such transfusions may influence hematologic parameters independently of granulocyte-colony stimulating factor administration and could represent an unmeasured confounding factor affecting neutropenia outcomes.

The lack of pharmacokinetic data, including blood levels of the administered drugs and their active metabolites, further limits the ability to directly assess the relationship between systemic drug exposure and observed toxicities. Finally, the study did not include survival analyses (progression-free survival and overall survival), which are crucial for understanding the long-term clinical effects of smoking status in patients treated with irinotecan.

Collectively, these limitations substantially affect the interpretation of our findings. In particular, the lack of pharmacokinetic and genotyping data prevents mechanistic confirmation, and the small subgroup sizes increase the risk of both false-negative and false-positive results. Therefore, our results should be considered preliminary and hypothesis-generating, and they warrant validation in larger prospective cohorts incorporating pharmacokinetic, genetic, and efficacy endpoints.

***Conclusion***

In this retrospective cohort, smoking status alone was not associated with significant differences in irinotecan-related toxicities. In contrast, exploratory subgroup analyses suggested that increasing smoking quantity was associated with a reduced incidence and severity of neutropenia, a finding that may reflect lower systemic exposure to the active metabolite SN-38 and raises concerns regarding potential reductions in treatment efficacy. These findings should be interpreted as hypothesis-generating and require confirmation in larger prospective studies incorporating pharmacokinetic, genetic, and efficacy endpoints. Nevertheless, they underscore the clinical importance of systematically documenting smoking behavior and actively encouraging smoking cessation as part of comprehensive supportive care in patients receiving irinotecan-based chemotherapy.

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## References


[1] de Man FM, Goey AK, van Schaik RH, et al. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics. Clin pharmacokinet. 2018;57:1229-54.

[2] Díaz-Villamarín X, Nieto-Sánchez MT, Martínez-Pérez M, et al. Dose-Limiting Toxicities and the Maximum Tolerated Dose of Irinotecan Based on UGT1A1 Genotypes: A Systematic Review. Pharmaceutics. 2025;17(5):542.

[3] Guemei AA, Cottrell J, Band R, et al. Human plasma carboxylesterase and butyrylcholinesterase enzyme activity: correlations with SN-38 pharmacokinetics during a prolonged infusion of irinotecan. Cancer Chemother Pharmacol. 2001;47(4):283-90.

[4] Rivory LP, Robert J. Molecular, cellular, and clinical aspects of the pharmacology of 20 (S) camptothecin and its derivatives. Pharmacol Ther. 1995;68(2):269-96.

[5] Haaz MC, Rivory L, Jantet S, et al. Glucuronidation of SN-38, the active metabolite of irinotecan, by human hepatic microsomes. Pharmacol Toxicol. 1997;80(2):91-6.

[6] Ciotti M, Basu N, Brangi M, et al. Glucuronidation of 7-ethyl-10-hydroxycamptothecin (SN-38) by the human UDP-glucuronosyltransferases encoded at the UGT1 locus. Biochem Biophys Res Commun. 1999;260(1):199-202.

[7] Ge S, Tu Y, Hu M. Challenges and opportunities with predicting in vivo phase II metabolism via glucuronidation from in vitro data. Curr Pharmacol Rep. 2016;2(6):326-38.

[8] Santos A, Zanetta S, Cresteil T, et al. Metabolism of irinotecan (CPT-11) by CYP3A4 and CYP3A5 in humans. Clin Cancer Res. 2000;6(5):2012-20.

[9] Yamamoto M, Kurita A, Asahara T, et al. Metabolism of irinotecan and its active metabolite SN-38 by intestinal microflora in rats. Oncol Reports. 2008;20(4):727-30.

[10] Yu J, Shannon WD, Watson MA, et al. Gene expression profiling of the irinotecan pathway in colorectal cancer. Clin Cancer Res. 2005;11(5):2053-62.

[11] Kehrer DF, Mathijssen RH, Verweij J, et al. Modulation of irinotecan metabolism by ketoconazole. J Clin Oncol. 2002;20(14):3122-9.

[12] Caraci F, Crupi R, Drago F, et al. Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metabol. 2011;12(6):570-7.

[13] Richards S, Umbreit JN, Fanucchi MP, et al. Selective serotonin reuptake inhibitor-induced rhabdomyolysis associated with irinotecan. Southern Med J. 2003;96(10):1031-4.

[14] Mori K, Kondo T, Kamiyama Y, et al. Preventive effect of Kampo medicine (Hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. Cancer Chemother Pharmacol. 2003;51:403-6.

[15] Mathijssen RH, Verweij J, De Bruijn P, et al. Effects of St. John's wort on irinotecan metabolism. J Natl Cancer Inst. 2002;94(16):1247-9.

[16] Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.

[17] Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.

[18] Cataldo JK, Dubey S, Prochaska JJ. Smoking cessation: an integral part of lung cancer treatment. Oncology. 2010;78(5-6):289-301.

[19] Nia PS, Weyler J, Colpaert C, et al. Prognostic value of smoking status in operated non-small cell lung cancer. Lung Cancer. 2005;47(3):351-9.

[20] Duffy SA, Khan MJ, Ronis DL, et al. Health behaviors of head and neck cancer patients the first year after diagnosis. Head Neck. 2008;30(1):93-102.

[21] Peppone LJ, Mustian KM, Morrow GR, et al. The effect of cigarette smoking on cancer treatment–related side effects. The oncologist. 2011;16(12):1784-92.

[22] Videtic GM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. J Clin Oncol. 2003;21(8):1544-9.

[23] Chellappan S. Smoking cessation after cancer diagnosis and enhanced therapy response: mechanisms and significance. Curr Oncol. 2022;29(12):9956-69.

[24] Parsons A, Daley A, Begh R, et al. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010;340.

[25] Yu Y-y, Jin H, Lu Q. Effect of polycyclic aromatic hydrocarbons on immunity. J Transl Autoimmun. 2022;5:100177.

[26] Luo K, Luo X, Cao W, et al. Cigarette smoking enhances the metabolic activation of the polycyclic aromatic hydrocarbon phenanthrene in humans. Carcinogenesis. 2021;42(4):570-7.

[27] Van der Bol JM, Mathijssen RH, Loos WJ, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol. 2007;25(19):2719-26.

[28] Elm Ev, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement: guidelines for reporting observational studies. 2008.

[29] Balogh EP, Dresler C, Fleury ME, et al. Reducing tobacco-related cancer incidence and mortality: summary of an institute of medicine workshop. The Oncologist. 2014;19(1):21-31.

[30] Burke L, Miller L-A, Saad A, et al. Smoking behaviors among cancer survivors: an observational clinical study. J Oncol Pract. 2009;5(1):6-9.

[31] Bardelmeijer HA, van Tellingen O, Schellens JH, et al. The oral route for the administration of cytotoxic drugs: strategies to increase the efficiency and consistency of drug delivery. Invest New Drugs. 2000;18(3):231-41.

[32] Ismail M, Khan S, Khan F, et al. Prevalence and significance of potential drug-drug interactions among cancer patients receiving chemotherapy. BMC Cancer. 2020;20:1-9.

[33] Riechelmann R, Girardi D. Drug interactions in cancer patients: A hidden risk? J Res Pharm Pract. 2016;5(2):77-8.

[34] van Leeuwen RW, Jansman FG, van den Bemt PM, et al. Drug–drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015;26(5):992-7.

[35] Riechelmann RP, Zimmermann C, Chin SN, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. Journal of pain and symptom management. 2008;35(5):535-43.

[36] Berg AK, Buckner JC, Galanis E, et al. Quantification of the impact of enzyme-inducing antiepileptic drugs on irinotecan pharmacokinetics and SN-38 exposure. J Clin Pharmacol. 2015;55(11):1303-12.

[37] Gilbert MR, Supko JG, Batchelor T, et al. Phase I clinical and pharmacokinetic study of irinotecan in adults with recurrent malignant glioma. Clin Cancer Res. 2003;9(8):2940-9.

[38] Kroon LA. Drug interactions and smoking: raising awareness for acute and critical care providers. Crit Care Nurs. Clinics. 2006;18(1):53-62.

[39] Pehlivan Z, Nural N. Prevalence of constipation in patients undergoing chemotherapy and the effect of constipation on quality of life. Support Care Cancer. 2022;30(10):8019-28.

[40] Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking and nicotine on cancer treatment. Pharmacotherapy. 2012;32(10):920-31.

[41] Dumez H, Guetens G, De Boeck G, et al. In vitro partition of irinotecan (CPT-11) in human volunteer blood: the influence of concentration, gender and smoking. Anticancer Drugs. 2005;16(8):893-5.