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Non-genetic Risk Factors for Colorectal Cancer in South Sulawesi: A Case-Control Study

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ABSTRACT

Using a case-control design, this investigation explored non-genetic determinants of colorectal cancer (CRC) among individuals in South Sulawesi. The participant pool comprised 89 cases and 84 controls, spanning ages 19 to 86, with 99 men and 74 women from multiple ethnicities. Univariate assessments employed chi-square, Fisher's exact test, t-test, and Mann-Whitney U test. A logit model with L1 regularization, adjusted for age, gender, and ethnicity, pinpointed noteworthy non-genetic risk factors. The variables scrutinized included patient weight, height, body mass index (BMI), site of defecation, physical activity, tobacco use, marital status, occupation, educational attainment, and proximity to the nearest healthcare facility. The odds ratio estimates from the logit model were used to evaluate the relevance of the identified risk factors. The logit model highlighted tobacco use, educational attainment, marital status, proximity to the nearest healthcare facility, and weight as meaningful risk factors. CRC cases exhibited a greater tendency toward lower education (OR = 1.819, 95% CI = 1.354–2.443), residence in distant areas (OR = 1.44, 95% CI = 1.17–1.772), and weight reduction (OR = 1.03, 95% CI = 1.013–1.048). Controls demonstrated a higher likelihood of being non-smokers (OR = 0.325, 95% CI = 0.149–0.707) and unmarried (OR = 0.161, 95% CI = 0.036–0.716). The findings established that additional non-genetic factors—namely, educational attainment, proximity to the nearest healthcare facility, weight, tobacco use, and marital status—also contributed to CRC incidence among the South Sulawesi population. The research underscored the importance of integrating these factors into subsequent, precisely directed CRC prevention efforts.

Keywords: Colorectal cancer, non-genetic, South Sulawesi population, Risk factors, Lifestyle, Socio-demographic

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Introduction

Colorectal cancer (CRC) represents an epithelial, solid malignancy that gives rise to both fatality and disease burden. Among its forms, adenocarcinoma predominates, comprising over 90% of all colorectal carcinoma diagnoses [1]. Anatomically, CRC encompasses malignancies of the colon and rectum. Its cellular origin remains a matter of dispute, centered on competing stochastic and cancer stem cell models and theories [2]. Owing to the notable similarities between carcinogenesis and colorectal development, it has been proposed that either residual fetal stem cells or mature colonic cells may be capable of transforming into cancer stem cells [3, 4]. Molecular controllers governing gut development, such as Nuclear β-catenin, Krüppel-like factor (KLF) proteins, Sonic Hedgehog, and the Notch-1 receptor, have been reported to be overexpressed in CRC [5-8]. Moreover, contemporary genome-wide association studies (GWAS) have uncovered acetaldehyde's function as a prognostic risk indicator tied to alcohol intake among light and moderate consumers [9], drawing attention to the robust interplay between environmental exposures and the molecular underpinnings of onco-pathogenesis.

Globally, 1,926,118 newly diagnosed colorectal cancer (CRC) cases were recorded in 2022, positioning CRC as the third most frequent cancer type by incidence; it simultaneously ranks second in lethality, having caused 903,859 deaths that year [10]. Although it has not yet become the most fatal cancer, both its incidence and mortality figures are climbing steeply compared to 2020 levels [11]. The emergence of early-onset CRC has also grown increasingly common [12-15]. Certain investigations pinpoint the anatomical location of these early-onset tumors in the distal colon [14] and rectal subsites [13]. Characteristically, individuals with early-onset CRC are commonly detected at more advanced disease stages relative to those with later-onset disease [16], with shifts in diet and lifestyle occurring between the 1950s and 1980s suspected as the principal driver [17].

While some studies document a decline in CRC incidence within particular regions [12-15, 18, 19], this pattern does not extend to numerous areas across Asia and Africa [20, 21], where many low- and middle-income countries (LMICs) are located. High-income countries (HICs) may report higher CRC incidence [10]. Yet, they record lower mortality rates than LMICs, a difference attributable to more health-conscious behaviors and widespread awareness of cancer screening, including fecal immunochemical tests (FIT) and fecal occult blood tests (FOBT) [22]. In LMICs, by contrast, deficient health infrastructure and workforce shortages obstruct these CRC screening measures, ultimately preventing reductions in both incidence and death rates [22]. Indonesia remains classified as an LMIC and continues to confront the CRC challenge. One report indicates that CRC in Indonesia manifests more frequently among males than females [23]. Other Indonesian CRC investigations have been organized either by geographic region [24-26] or by ethnicity [27], reflecting the nation's heterogeneous demographic composition. Such diversity calls for an all-encompassing approach to uncover distinct risk profiles tailored to each population segment.

Prompted by the well-documented connection between environmental and genetic determinants, this study set out to link and elucidate how non-genetic variables interrelate in contributing to CRC development through a case-control framework, with a specific focus on the South Sulawesi population. A GWAS examining this same demographic had been undertaken earlier [28]. Non-genetic factors had been superficially addressed in prior work, though the scope was restricted to dietary intake measures [29]. The present study extended the inquiry to additional non-genetic factors, including participant health, socioeconomic status, and daily behavioral routines, aiming to pinpoint those factors significantly correlated with CRC occurrence. By doing so, this investigation provided valuable insights into the formulation of targeted CRC prevention strategies for the South Sulawesi population.

Materials and Methods

Patient data collection

The dataset employed in this study matched the observations used in Yusuf *et al*. [28] and Nurlaila *et al*. [29]. Cases consisted of patients confirmed to have CRC, with eligibility validated through clinical examinations. Case recruitment took place across seven hospitals: Grestelina Hospital, Wahidin Sudirohusodo Hospital, Akademis Hospital, Hasanuddin University Hospital, Stella Maris Hospital, Hikmah Hospital, and Ibnu Sina Hospital, all situated within Makassar City. Controls comprised individuals without a CRC diagnosis. This control cohort was frequency-matched to the case cohort according to age, ethnicity, and gender. Each participant underwent an in-person interview and completed an extensive questionnaire addressing demographic details, family history, smoking patterns, alcohol use, and a summary of dietary consumption. For the case group, clinical and histopathological findings were also recorded. Altogether, the case questionnaire contained 382 items, while the control version included 319.

Despite all samples originating from hospitals within Makassar, the recruited patients reflected a broad array of ethnic backgrounds from South Sulawesi and beyond. Initially, the study recruited 162 cases and 193 controls. Nevertheless, a subset of participants declined to answer several follow-up questions, resulting in numerous missing values. Those records were omitted from the analysis. The finalized sample set, therefore, contained 173 patients, comprising 89 cases and 84 controls.

Statistical analysis

From the set of risk factors compiled in Lukman *et al*. [27] and Yusuf *et al*. [28], those related to participant health, behavioral patterns, and socioeconomic markers were selected for analysis. Health-associated variables included tobacco use, body mass index (BMI), weight, and height. Factors linked to socioeconomic circumstances

and everyday routines encompassed proximity to the nearest healthcare facility, marital status, occupation, place of defecation, and educational attainment. The variable capturing proximity to the nearest healthcare facility had missing entries, which were estimated using linear regression informed by other variables, deliberately excluding CRC status to avert circular reasoning. While this imputation retained the sample size, it failed to account for the variance of the absent data and the underlying randomness mechanism, thereby introducing potential bias. Nonetheless, given that the fraction of missing entries was relatively modest (~7%), the resulting bias was considered negligible in its overall effect.

For the univariate stage, nominal risk factors were evaluated via the chi-square test [30]. Where chi-square test assumptions were violated, Fisher's exact test was employed as an alternative [30]. Continuous risk factors were principally assessed using the t-test [31]. In situations where the risk factor exhibited an ordinal distribution or where t-test assumptions were not fulfilled, the Mann-Whitney U test [32] was substituted. A multivariate evaluation followed, using a logit model with L1 regularization [33] to extract meaningful non-genetic risk factors based on non-shrinking coefficients. Age, sex, and ethnicity were included in the logit model as baseline covariates. The pool of L1 regularization coefficient (C) candidates spanned values from 0 to 1, representing inverse regularization intensity. As C approached 0, coefficient shrinkage became more aggressive, thereby retaining fewer risk factors. The candidate achieving the highest average F1-score across 10-fold cross-validation was selected as the optimal C. All statistical tests performed were two-tailed, employing a significance threshold of $P = 0.05$.

Results and Discussion

Summary of collected samples

The distribution of males and females did not differ between the case and control arms ($P > 0.999$). The ages ranged from 19 to 86 years, and the case arm had a mean age of 53.1 years, while the control arm had a mean age of 50.5 years ($P = 0.12$). The self-declared ethnic composition was similarly balanced across the two arms, with individuals of Bugis and Makassar descent predominating in both ($P = 0.86$). Other local ethnicities represented included Mandar, Toraja, Palu, and Kolaka, as well as ethnic groups from beyond South Sulawesi who live in Makassar City.

When considering health-related parameters, a significant difference in average body weight was observed ($P < 0.001$), whereas no meaningful difference in body height was detected ($P = 0.35$). The proportion of individuals who smoked was larger within the case arm ($P < 0.001$). Engaging in exercise was uncommon among participants in both arms ($P = 0.176$). Individuals in the control arm benefited from shorter travel distances to the nearest health center relative to the case arm ($P < 0.001$). Resorting to a location other than a lavatory for defecation was strongly associated with elevated CRC occurrence ($P < 0.001$). Marital status also showed a significant association with CRC occurrence ($P = 0.007$), with married individuals comprising a greater share of the CRC arm. As for educational attainment, both arms showed roughly equivalent distributions across all tiers, leaving this factor below the threshold of significance ($P = 0.493$). A comparable situation was observed for occupation across the two arms ($P = 0.51$). Univariate testing revealed that body weight, smoking behavior, defecation site, marital status, and proximity to the nearest health center each showed a substantial relationship with CRC occurrence, with P-values < 0.001 in all cases except marital status, where $P = 0.007$. For continuous risk factors evaluated using the Mann-Whitney U test, the median and standard deviation are reported in addition to the mean and standard deviation.

Significantly-associated non-genetic risk factors

One-hot encoding was applied to the nominal risk factors before they entered the model. In contrast, ordinal risk factors—which embody a meaningful sequence—were handled via label encoding, where higher assigned values corresponded to higher tiers. Gender, ethnicity, defecation site, marital status, smoking behavior, and occupation were nominal factors; exercise behavior and educational attainment were ordinal factors. The occupation category of fisherman triggered quasi-separation and was therefore removed from the analysis. In the optimization routine, the L1 logit model with $C = 0.08$ achieved the peak F1-score of 75.5%. Although models with C values above 0.08 incorporated a broader array of risk factors, they returned diminished average F1 scores **(Figure 1).** At the same time, models with C values below 0.08 proved overly parsimonious, with every risk factor coefficient collapsing to zero when $C = 0.01$.

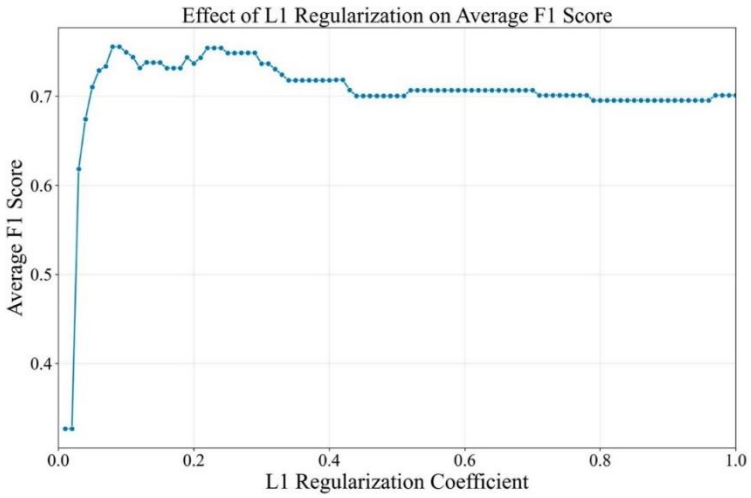

Figure 1. Regularization coefficient alongside its average F1 score derived from 10-fold cross-validation.

Further diagnostic evaluation of the L1 logit at C = 0.08 is conveyed through the Area Under the Curve (AUC) metric for each Receiver Operating Characteristic (ROC) plot **(Figure 2).** Each ROC trace corresponds to one fold in the C = 0.08 configuration. AUC values varied across the cross-validation folds, ranging from 0.74 in the fourth fold to 0.97 in the sixth fold. As **Figure 2** illustrates, the mean AUC computed across the 10-fold cross-validation is 0.85, with a standard deviation of merely 0.07. This average AUC underscores the L1 logit model's capacity to reliably distinguish CRC cases from controls in the study population, particularly at C = 0.08 and despite the constrained sample size. The risk factors retained by the L1 logit at C = 0.08 were subsequently refitted within an unregularized logit framework **(Table 1)** to compute the odds ratios.

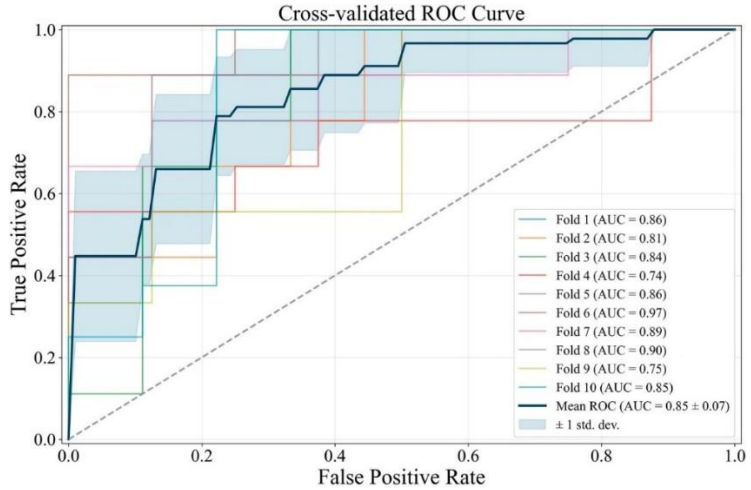

Figure 2. ROC curve for the L1 logit with C = 0.08.

Table 1. Logit summary for the refitted risk factors.

Risk factors	P-value	Standard deviation	Coefficient
Weight	< 0.001[a]	0.008	0.030
Smoking Habit			
No	0.005[a]	0.397	−1.125
Marital Status			
Married	0.017[a]	0.763	−1.830
Education Level	< 0.001[a]	0.151	0.598
Distance to Nearest Health Center	0.001[a]	0.106	0.364

[a]: marks a statistically meaningful difference between the case and control arms for that specific variable.

The effect measure plot illustrating the odds ratios appears in **Figure 3.** Each 1-kg increase in a patient's weight was associated with a 3% increase in the odds of CRC. Patients who did not maintain a regular smoking practice showed a 67.5% reduction in the odds ratio. Those from lower educational strata had an odds ratio of 81.9 for CRC. Married status corresponded to an 83.9% decline in the CRC occurrence odds ratio. Each additional kilometer separating a patient from the nearest health center was associated with an 81.9% increase in the odds of CRC. None of the adjustment variables demonstrated any relationship with CRC occurrence in the South Sulawesi population.

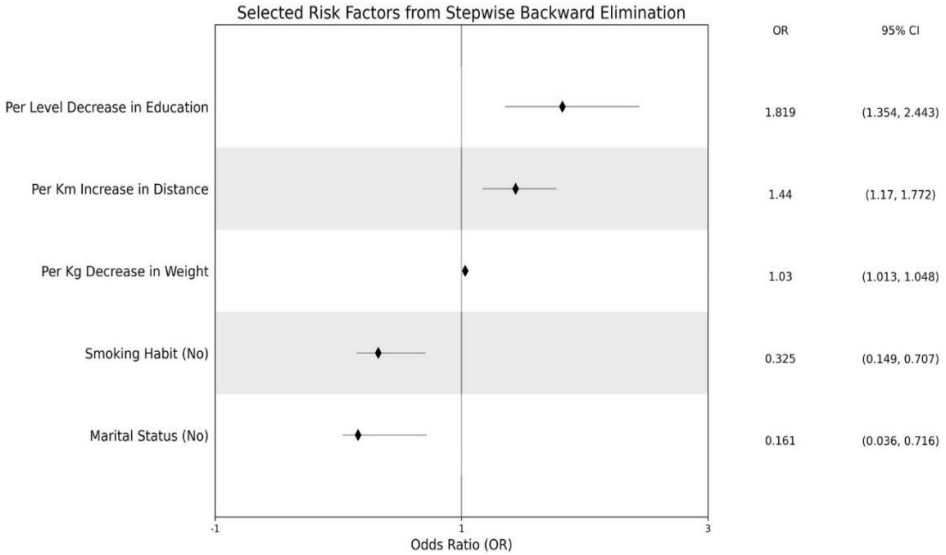

Figure 3. Effect measure plots for the significantly-associated risk factors.

Within a wide range of studies encompassing diverse populations, tobacco consumption—whether firsthand or secondhand—has been repeatedly linked to CRC [20, 34, 35]. This relationship receives further genetic corroboration from the discovery of an implicated SNP in the cell adhesion molecule 2 (CADM2) gene, particularly among carriers of the GG and GA alleles, which heightens CRC vulnerability [36]. In light of these observations, the prominent connection between smoking behavior and CRC occurrence detected in the South Sulawesi population—where the lack of smoking practice reduces CRC probability (OR = 0.325; 95% CI = 0.149–0.707) **(Figure 3),** and vice versa—is both consistent and unsurprising. Within the current study specifically, a chi-square test crossing gender with smoking practice revealed that tobacco use was substantially more prevalent among males ($P < 0.001$), a finding consistent with the same demographic pattern reported in other investigations of tobacco consumption in the South Sulawesi setting [37, 38].

Nonetheless, because educational attainment is incorporated into the logit model as an ordinal variable, a Mann-Whitney U test was also conducted to compare the distributions of educational levels across the two arms. When applied to the ordinal education data, the Mann-Whitney U test revealed a difference in central tendency, with the control arm's typical education level at senior high school graduate status, compared with junior high school graduate status in the case arm ($P = 0.007$). The literature offers no unified conclusion on the relationship between education level and CRC incidence. An investigation conducted in another Indonesian region notes that socioeconomic determinants, including higher educational attainment, tend to lower the odds of CRC [39]. The elevated odds ratio associated with education level in the current study (OR = 1.819; 95% CI = 1.354–2.443) **(Figure 3)** reveals a preponderance of CRC among patients with limited education, a pattern that resonates with findings from certain other countries [40, 41]. Even so, opposing trends have been documented elsewhere [42, 43].

Analogous to education level, marital status (OR = 0.161; 95% CI = 0.036–0.716) demonstrates a heterogeneous pattern of association with CRC occurrence across previous reports, without elucidation of the potential confounding factor when a link is present [41, 44]. When the lens is shifted to dietary intake risk factors [29], however, the confounder arising from marital status in this investigation is the intake of reheated food (Fisher's exact $P = 0.012$). Married individuals consume reheated meals more regularly (Chi-square = 0.007). Among unmarried individuals, this tendency is not evident (Fisher's exact $P = 0.25$) (**Table 2).** It is conjectured that

married patients residing in Makassar City, who tend to be older than unmarried patients (Mann-Whitney U P < 0.001), may turn to reheated food to expedite meal preparation or due to other economic pressures, such as infrequent grocery replenishment. Nevertheless, owing to the data thinness within the unmarried segment, a deeper exploration of dietary habits among older patients remains necessary.

Table 2. Contingency table cross-referencing marital status and reheated food consumption.

Marital status	Reheated foods consumption	CRC incidence		P-value	Univariate test
		Yes	No		
Married	Seldom	23	57	0.007[a]	Chi-square
	Often	63	10		
Unmarried	Seldom	2	9	0.25	Fisher's exact
	Often	1	0		

[a]: marks a statistically meaningful difference between the case and control arms for that specific variable.

Individuals living in outlying areas around Makassar City face limited access to healthcare services, particularly those equipped with comprehensive capabilities, which increases the likelihood of CRC (OR = 1.44; 95% CI = 1.17–1.772). Top-tier healthcare establishments within Makassar City, as drawn from Google review data, are heavily concentrated in the subdistricts of Rappocini, Panakkukang, Mariso, Manggala, Ujung Tanah, and Makassar proper [45], all lying in Southwest Makassar, the urban core. Hence, the geographic spread is lopsided, with the standard and density of healthcare assets in Southwest Makassar outperforming and heavily outnumbering those in Tamalanrea and Biring Kanaya—two of the most populous subdistricts in Northeast Makassar that also retain a rural character. A case-control study involving separate populations has lent weight to the notion [41] that rural residence contributes substantially to CRC risk. Meanwhile, a study on colon cancer incidence in Yogyakarta, another Indonesian province, found no notable effect of rural versus urban residence on CRC incidence [26]. Yet, unlike the circumstances in Makassar City, Yogyakarta's healthcare framework, above all its hospital system, offers extensive coverage even in rural areas [46]. Beyond enjoying less obstructed access to health center amenities, urban-based patients are also typically more cognizant of CRC screening and preventive practices, as substantiated by investigations from other geographies [47, 48].

A reverse-direction relationship emerged between body weight and CRC occurrence (OR = 1.03; 95% CI = 1.013–1.048), diverging from what a multitude of earlier inquiries have reported [49, 50]. The reversal, however, is attributable to the fact that patient weight was captured late—only after the individual had already been diagnosed with CRC stage III or IV—a point likewise observed in our earlier work [28, 29].

Guided by the identified risk factors, future CRC screening drives in Makassar City would do well to focus on residents with limited educational backgrounds and those living in rural areas where healthcare reach is limited. These two determinants should also serve as a warning to governing bodies about economic and health infrastructure imbalances across the territory, which facilitate ailments such as CRC. Area health agencies ought to reinforce communications around the hazards of tobacco use and the benefits of quitting, the perils tied to repeated consumption of reheated meals, and the value of periodic health examinations to enable the early identification and prevention of CRC.

Conclusion

As the first effort to probe non-genetic CRC risk factors among the South Sulawesi population, this study identified relevant non-genetic factors influencing CRC incidence in South Sulawesi, with particular attention to Makassar City. A multivariate logit model was used to identify significant risk factors for CRC incidence in this population, while controlling for patient age, gender, and ethnicity. Among the health, socioeconomic, and behavioral risk factors entered into the model, those that emerged as significantly associated were smoking habit, educational attainment, proximity to the nearest health center, marital status, and patient weight. Lower educational tiers intensified the likelihood of CRC development in the population. Unwholesome dietary behavior revolving around reheated food served as the principal explanatory pathway underpinning the relevance of marital status as a risk factor, given that married patients resorted to reheated meals more habitually than unmarried ones. Echoing other works that have connected persistent smoking to CRC, tobacco use was likewise validated as a significant risk factor.

Furthermore, mirroring the asymmetrical distribution of health center availability in select zones surrounding Makassar City, individuals residing in rural areas had elevated odds of CRC. Initially, reduced weight appeared as a significant factor; however, this finding was driven by delayed collection of weight and BMI data rather than representing an independent risk factor. The defecation site also lost significance in the multivariate evaluation. No link was established in this population between CRC incidence and the remaining risk factors, such as exercise practices and occupational category.

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Conflict of Interest: None

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Ethics Statement: The Hasanuddin University Ethical Committee approved the studies involving humans with registration number UH 15040389. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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