META-ANALYSIS

The first combined meta-analytic approach for elucidating the relationship of circulating resistin levels and RETN gene polymorphisms with colorectal and breast cancer

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Abstract

Background: Evidence suggests that circulating resistin levels are altered in colorectal cancer (CRC) and breast cancer (BC). Again, polymorphisms in resistin-encoding gene RETN have been evaluated in CRC and BC. However, there is a scarcity of data establishing the relationship of resistin and RETN polymorphisms (rs1862513 and rs3745367) with these cancers. This study aimed to analyze the relationship of resistin levels and RETN polymorphisms with CRC and BC in a combined meta-analytic approach.

Main body of the abstract: After a comprehensive online literature search, screening and eligibility check, 41 articles (31 with resistin level and 10 with RETN polymorphisms) were retrieved for meta-analyses. The mean difference (MD) of resistin was calculated and pooled to investigate the effect sizes with a 95% confidence interval (CI), and the connection of genetic polymorphisms was analyzed with an odds ratio (OR) and 95% CI. The analysis showed that resistin level is significantly higher in CRC (MD = 3.39) and BC (MD = 3.91) patients. Subgroup analysis in CRC showed significantly higher resistin in serum (MD = 4.61) and plasma (MD = 0.34), and in BC, a significantly elevated resistin level was reported in premenopausal (MD = 7.82) and postmenopausal (MD = 0.37) patients. Again, RETN rs1862513 showed a significantly strong association with CRC (codominant 1 — OR 1.24, codominant 2 — OR 1.31, dominant model — OR 1.25, and allele model — OR 1.16) and with BC (codominant 2 — OR 1.51, codominant 3 — OR 1.51, recessive model — OR 1.51, and allele model — OR 1.21). RETN rs3745367 did not show any association with these cancers.

Short conclusion: Overall, our analysis indicates that higher circulating resistin levels are associated with an elevated risk of CRC and premenopausal and postmenopausal BC. Besides, rs1862513 in RETN gene is significantly connected with both CRC and BC.

Keywords: Resistin, RETN, Breast cancer, Colorectal cancer, Meta-analysis

Background

Colorectal cancer (CRC) is a frequently occurred malignancy throughout the world. It is consistently placed among the top three cancers based on morbidity and mortality rates [1, 2]. It is a public health concern worldwide, particularly in developed countries, where the incidence rate (about 18%) is higher than the developing or under-developed countries. In the past few decades, the percentage of CRC cases are rapidly increasing in developing regions. This is considered a complex multi-pathway malignancy associated with a chronic inflammatory reaction, metabolic syndrome, obesity, and insulin resistance. Recent evidence suggests that adipocyte-secreted factors such as resistin, adiponectin, visfatin, leptin, and various cytokines (IL-6, IL-10, TNF-α,
In terms of incidence, breast cancer (BC) has been the leading malignancy among women worldwide. It is also one of the most common causes of mortality, comprising almost 6.6% of all cancer-related deaths. Statistics showed that about 2.1 million BC cases were recorded in 2018, leading to the death of 626,679 patients [5, 6]. BC is a heterogeneous and polygenic multifactorial disease that occurs due to the combined effect of multiple factors, including genetic and epigenetic abnormalities, unhealthy lifestyle, and environmental pollutants [7]. Taking high-fat diets, physical inactivity, early menopausal cycle, late menopause, denser breast tissues, age, hormonal imbalance or exogenous hormone therapy, radiation therapy, high mental stress, and exposure to environmental pollutants are the common causes of BC [8].

Resistin, also known as an adipocyte-secreted factor, is a 12.5 kDa cysteine-rich 108-amino-acid peptide adipocytokine secreted by adipocytes and monocytes [9]. This inflammatory protein was first identified in mice adipose tissue and subsequently named resistin due to its role in insulin resistance [10]. Translational studies revealed that human resistin is primarily secreted from macrophages rather than from adipocytes [11]. The adipokine resistin belongs to the family of resistin-like molecules (RELM) and is commonly localized in inflammatory zone 3 [10, 12]. Resistin is one of the most common candidate molecules that play a significant role in numerous physiological and pathological processes in human body. Accumulating evidence suggests that this cytokine exhibits inflammatory, autoimmune, metabolic, proliferative, angiogenic, and metastatic properties via multiple cellular and molecular pathways [1, 13].

Although resistin was initially investigated for a functional role in insulin resistance and obesity, its diverse role in different diseases has drawn the concentration of researchers, making it one of the most studied biomarkers. Serum levels of resistin have been implicated in the occurrence and progression of various inflammatory processes, such as atherosclerosis, diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, inflammatory bowel disease, rheumatic arthritis, and malignant tumors [1, 13, 14]. Elevated concentration of resistin in plasma acts as a prognostic biomarker in the progression and metastasis of breast, colorectal, ovarian, pancreatic, lung, endometrial, prostate, and other obesity-related cancers in human. High serum resistin level was also found to be strongly associated with tumor stage and poor survival [15, 16]. Previous studies reported a significantly higher concentration of serum resistin in BC patients. Moreover, enhanced expression of serum resistin in BC tissues was found to be correlated with postmenopausal BC and poor tumor prognosis [17]. Again, increased circulating resistin levels in CRC have also been documented by previous studies. However, there is a gap in the consistency of previously published results on the association of serum resistin level with BC and CRC risk, which should be clarified.

Resistin is encoded by RETN, an important adipocytokine gene located on chromosome 9 (19p13.3) and mainly expressed in adipocytes [18, 19]. Previous investigations on RETN genetic polymorphisms reported their strong correlation with circulating resistin levels, RETN expression, and body mass index (BMI) [20, 21]. Single nucleotide polymorphisms (SNPs) are generally spotted in the promoter region and 3′-untranslated region of RETN [22]. Common SNPs in the RETN gene, including promoter rs1862513 (C-180G/ C-420G) and rs3745367 (G+299A), have been previously analyzed for their contribution to the progression of several diseases, including CRC [19, 21, 23–25] and BC [18, 22]. However, the outcomes of these studies remained conflicting and need to be re-evaluated.

To date, numerous case-control studies have been carried out in different ethnic groups to examine the correlation of resistin levels and RETN gene polymorphisms with multiple cancers, especially with CRC and BC. However, these findings remained inconclusive and inconsistent. To our knowledge, no previous systemic review and meta-analysis was conducted to evaluate the relationship between both circulatory resistin and RETN gene polymorphisms and these cancers. Therefore, we performed the first combined meta-analyses to establish a comprehensive relationship of resistin levels in serum or plasma and RETN genetic polymorphisms with CRC and BC.

**Results**

**Description of the included studies**

Our literature search generated a total of 2674 publications in PubMed, ScienceDirect, BMC, EMBASE, Cochrane Library, Web of Science, and Google Scholar databases for both meta-analyses shown in Fig. 1. Following the removal of duplicates and studies analyzing biomarkers other than resistin and polymorphisms other than RETN, 579 records remained for the title and abstract screening. Due to the lack of full-text access and excluding reviews, commentaries, or studies with inadequate data, 41 articles remained for both qualitative and quantitative analysis (meta-analysis) among which 31 for resistin level and 10 for RETN genetic association.

Of 31 articles with resistin levels, a total of 16 studies were on CRC [11, 25–39], and 15 studies were on BC [18, 40–53]. Among the 16 studies on CRC, 9 studies [25–33] analyzed the serum resistin in 382 CRC cases
and 367 controls, whereas 7 studies [11, 34–39] analyzed the plasma resistin in 1199 CRC cases and 1492 controls. Again, among 15 studies in analyzing resistin level in 2132 BC patients and 1780 controls, only two studies [24, 51] analyzed the plasma resistin level in 916 cases and 864 controls, while 13 studies [18, 40–48, 50, 52, 53] analyzed serum resistin level in 1216 cases and 916 controls. The characteristics of the selected studies evaluating resistin level with CRC and BC are summarized in Tables 1 and 2, respectively.

Again, of 41 studies, 10 studies evaluated the association of \textit{RETN} gene polymorphisms with CRC and BC. Six studies examined the association of rs1862513 on CRC [19, 21, 24, 25, 38, 54] and 3 studies examined the correlation of rs1862513 on BC [18, 22, 55] that included a total of 2095 cases and 2385 controls. For rs3745367, only three eligible studies were found with 747 cases and 791 controls, among which two studies were on CRC [21, 23] and one with BC [22]. Table 3 represents the characteristics of selected studies evaluating \textit{RETN} gene polymorphisms.

**Meta-analysis of resistin levels and link with CRC and BC**

According to our meta-analysis of 31 studies, the levels of resistin in both CRC and BC patients are significantly higher than those in the control groups, as illustrated in Figs. 2 and 3, respectively. The results of the meta-analysis revealed that the resistin level was significantly higher in CRC patients than in controls when using a random effect model (MD = 3.39, 95% CI = 2.23–4.54, \(p<0.00001\)). Again, in terms of BC, patients had a significantly higher level of resistin than controls (MD = 3.91, 95% CI = 1.12–6.71, \(p=0.006\)) and the difference was statistically significant.
Table 1  Characteristics of the selected studies evaluating resistin level with colorectal cancer in the meta-analysis

| Study ID          | Country | Cases/controls | Assay type | Kit provider         | Mean resistin level (ng/ml) ± SD | NOS score |
|-------------------|---------|----------------|------------|----------------------|----------------------------------|-----------|
| Serum             |         |                |            |                      | Cases                           | Controls  |
| Al-Harithy et al. [25] | KSA     | 60/60          | ELISA kit  | ALPCO Diagnostic     | 19.44 ± 8.46                     | 5.45 ± 2.73 | 7         |
| Danese et al. [26] | Italy   | 40/40          | ELISA kit  | Medigagnost          | 9.99 ± 15.76                     | 4.98 ± 4.92 | 8         |
| Gonullu et al. [27] | Turkey  | 36/37          | ELISA kit  | BioSource            | 6.1 ± 3.3                        | 4.5 ± 1.5  | 8         |
| Joshi et al. [28]  | South Korea | 100/100       | ELISA kit  | Adipogen             | 4.9 ± 2.3                        | 2.8 ± 1.7  | 8         |
| Kosova et al. [29] | Turkey  | 20/20          | ELISA kit  | Millipore Corporation | 4.92 ± 2.2                      | 3.39 ± 1.1 | 7         |
| Kumor et al. [30]  | Poland  | 36/25          | ELISA kit  | R&D Systems          | 6.79 ± 2.41                      | 3.6 ± 1.08 | 7         |
| Lu et al. [31]     | China   | 30/30          | ELISA kit  | ADL                  | 7.72 ± 2.6                       | 7.42 ± 3.7  | 7         |
| Shafik et al. [32] | Egypt   | 30/25          | ELISA kit  | AssayMax™            | 18.86 ± 2.6                      | 9.55 ± 1.4  | 7         |
| Tulubas et al. [33] | Turkey  | 30/30          | ELISA kit  | AssayMax™            | 18.77 ± 5.09                     | 13.36 ± 6.36 | 8         |
| Total             |         | 382/367        |            |                      |                                 |           |
| Plasma            |         |                |            |                      |                                 |           |
| Farahani et al. [34] | Iran  | 82/88          | ELISA kit  | ZellBio              | 5.7 ± 1.2                        | 5.4 ± 1.3  | 8         |
| Hillenbrand et al. [35] | Germany | 67/60         | Multiplex Assay | Millipore           | 19.53 ± 29.58                    | 13.63 ± 14.96 | 7         |
| Ho et al. [36]    | USA     | 456/834        | Multiplex Assay | Millipore          | 13.03 ± 4.83                     | 12.57 ± 4.31 | 8         |
| Mihajlovic et al. [11] | Serbia | 86/75         | ELISA kit  | R&D Systems          | 20.72 ± 10.62                    | 12.08 ± 7.58 | 7         |
| Nakajima et al. [37] | Japan  | 115/115       | ELISA kit  | BioVender            | 4.67 ± 2.48                      | 3.33 ± 1.88 | 8         |
| Wågsäter et al. [38] | Sweden | 35/34         | ELISA kit  | R&D Systems          | 2.62 ± 0.70                      | 3.42 ± 0.77  | 7         |
| Zhao et al. [39]   | China   | 358/286        | ELISA kit  | Biovision Inc        | 8.03 ± 4.99                      | 5.69 ± 3.18 | 8         |
| Total             |         | 1199/1492      |            |                      |                                 |           |

NOS, Newcastle–Ottawa Scale

When we stratified the studies on CRC by the sample sources (serum and plasma), 9 studies offered relevant data for serum resistin level, and 7 studies offered relevant data for plasma resistin level, shown in Fig. 2. Subgroup analysis in CRC revealed that the serum resistin level was significantly higher in patients compared to controls (MD = 4.61, 95% CI = 2.32–6.91, p < 0.0001), whereas a higher level of plasma resistin was also found in patients compared to controls (MD = 0.34, 95% CI = 0.13–0.54, p = 0.001). In CRC patients, the mean difference of resistin is higher in serum samples than in plasma samples (serum vs. plasma: MD = 4.61 vs. MD = 0.34).

Again, when the studies on BC studies were stratified by menopausal status, 5 studies offered relevant data for premenopausal women, and 9 studies offered relevant data for postmenopausal women, depicted in Fig. 3. The mean difference of resistin level found for premenopausal women was significantly higher compared to premenopausal controls (MD = 7.82, 95% CI = 7.46–8.19, p < 0.00001), and for postmenopausal women the level of resistin was also higher in comparison with postmenopausal controls (MD = 0.37, 95% CI = 0.21–0.54, p < 0.00001). The mean difference of resistin is higher in premenopausal women than in postmenopausal women (premenopausal vs. postmenopausal: MD = 7.82 vs. MD = 0.37). From the funnel plot analysis for detecting the association of resistin (Fig. 7), we did not find any notable asymmetry for CRC and BC.

Meta-analysis of RETN polymorphisms and link with CRC and BC

Table 4 shows the association of RETN genetic polymorphisms with CRC and BC. Analysis of RETN rs1862513 polymorphism in CRC revealed that four genetic association models including codominant 1 (GC vs. CC), codominant 2 (GG vs. CC), dominant model (GG + GC vs. CC), and allele contrast (G vs. C) are associated with significantly enhanced risk of CRC (OR 1.24, 95% CI 1.16–1.30; p = 0.007; OR 1.31, 95% CI 1.018–1.69; p = 0.012, respectively) (Fig. 4). Again, analysis of rs1862513 polymorphism in BC also showed significantly strong association in codominant 2 (GG vs. CC), codominant 3 (GG vs. GC), recessive (GG vs. GC + CC), and allele (G vs. C) models (OR 1.51, 95% CI 1.12–2.03; p = 0.007; OR 1.51, 95% CI 1.12–2.04; p = 0.007; OR 1.51, 95% CI 1.15–1.99; p = 0.004; and OR 1.21, 95% CI 1.05–1.40, p = 0.008, respectively) (Fig. 5).
The meta-analysis of the RETN rs3745367 polymorphism in CRC and BC, on the other hand, found no statistically significant link in any genetic model (Figs. 6, 7). Funnel plots for detecting the link of RETN rs1862513 and rs3745367 polymorphisms with CRC and BC are depicted in Fig. 8. However, no significant asymmetry was found.

**Publication bias, heterogeneity, and sensitivity analysis**

We also analyzed the publication bias for both CRC and BC with resistin level, as shown in Table 5. In the case of CRC, Egger's $p$-value was found to be significant (0.044), but the Begg-Mazumdar $p$-value was statistically not significant (0.280) for the overall sample (serum and plasma). However, no significant publication bias was found in subgroup analysis for serum and plasma resistin levels ($p > 0.05$ for both). Again, a significant publication bias was observed in overall BC samples (Egger's $p$-value: 0.0005 and Begg-Mazumdar $p$-value: 0.015), but in terms of premenopausal BC patients, neither Egger’s test ($p = 0.075$) nor Begg-Mazumdar’s test ($p = 0.624$) showed a statistically significant publication bias. However, for postmenopausal women, Egger’s $p$-value was significant (0.005) though the significance was not observed with Begg-Mazumdar $p$-value (0.532). We also found a significant heterogeneity ($p < 0.00001$) across the overall analysis of studies with resistin level in both CRC and BC as well as subgroup analysis according to the menopausal status of subjects (premenopausal and postmenopausal) in BC and sources of the sample (serum or plasma) in CRC (Figs. 2 and 3).

In terms of RETN polymorphisms with the risk of CRC and BC, negligible publication bias was reported (Table 4). Begg-Mazumdar’s $p$-value in the recessive model (0.039) and Egger's $p$-value in allele model (0.033) were significant in CRC and BC, respectively, for rs1862513 polymorphism. Only Egger's $p$-value in allele model (0.042) for rs3745367 was found to be significant. No other publication bias was found. Again, heterogeneity analysis showed that for rs1862513, only codominant model 3 (0.038) with CRC and for rs3745367 codominant 1 (0.029), dominant (0.041), and overdominant model

| Study ID       | Country | Sample source | Sample type | Cases/controls | Assay type | Kit provider | Mean resistin level (ng/ml) ± SD | NOS score |
|---------------|---------|---------------|-------------|---------------|------------|-------------|---------------------------------|-----------|
| Ahmed [40]    | Iraq    | Serum         | Premenopausal | 90/90         | ELISA kit  | Bio-Rad Laboratories | 18.32 ± 2.4 | 3.5 ± 0.5 | 7                     |
| Alokail et al. [41] | KSA   | Serum         | Both         | 56/53         | ELISA kit  | Immunodiagnostik   | 18.9 ± 1.2 | 15.2 ± 1 | 7                     |
| Aly et al. [42] | KSA   | Serum         | UD           | 35/40         | ELISA kit  | Invitrogen         | 4.42 ± 0.47 | 1.84 ± 2.35 | 7                   |
| Assiri & Kamel [43] | KSA   | Serum         | Postmenopausal | 110/89       | ELISA kit  | R&D systems        | 26.24 ± 1.95 | 22.63 ± 3.99 | 8                   |
| Assiri et al. [44] | KSA   | Serum         | Both         | 82/68         | ELISA kit  | R&D systems        | 26.24 ± 1.59 | 22.69 ± 2.58 | 8                   |
| Crisóstomo et al. [45] | Portugal | Serum         | Both         | 77/77         | ELISA kit  | Duo Set ELISA      | 14.58 ± 10 | 10.86 ± 8.55 | 8                   |
| Dalamaga et al. [46] | Greece | Serum         | Postmenopausal | 102/102       | ELISA kit  | Avibion            | 11.2 ± 6.4 | 7.7 ± 4.85 | 8                   |
| Dalamaga et al. [47] | Greece | Serum         | Postmenopausal | 103/103       | ELISA kit  | Avibion            | 11.24 ± 6.4 | 7.73 ± 4.85 | 8                   |
| Georgiou et al. [48] | Greece | Serum         | Both         | 157/52        | ELISA kit  | BioVendor           | 6.09 ± 3.08 | 6.16 ± 1.85 | 7                   |
| Gunter et al. [49] | USA    | Plasma        | Postmenopausal | 875/821       | ELISA kit  | EMD Millipore      | 12.1 ± 1.8 | 12.3 ± 1.93 | 8                   |
| Hou et al. [50] | China   | Serum         | Both         | 80/50         | ELISA kit  | R&D systems        | 26.35 ± 5.36 | 23.32 ± 4.75 | 7                   |
| Kang et al. [51] | Korea   | Plasma        | Both         | 41/43         | ELISA kit  | AdipoGen           | 5.23 ± 6.9  | 1.46 ± 2  | 8                   |
| Muñoz-Palomique et al. [18] | Mexico | Serum         | Postmenopausal | 20/40       | ELISA kit  | Preprotech Kit     | 10.60 ± 2.08 | 8.26 ± 2.38 | 7                   |
| Patrício et al. [52] | Portugal | Serum         | Both         | 64/52         | ELISA kit  | Duo Set ELISA      | 17.30 ± 12.6 | 11.60 ± 11.4 | 8                   |
| Wang et al. [53] | Taiwan  | Serum         | UD           | 240/100       | ELISA kit  | eBioscience        | 32.72 ± 13.42 | 27.36 ± 5.49 | 7                   |
| Total         |         |               |              | 2132/1780     |            |              |                                |           |
| Study ID         | Year | Country | Cancer type | Genotyping method | Cases | Controls | Cases | Controls | NOS score |
|------------------|------|---------|-------------|-------------------|-------|----------|-------|----------|-----------|
|                  |      |         |             |                   | GG    | GG       | GG    | GG       |           |
| **RETN rs1862513** |      |         |             |                   |       |          |       |          |           |
| Al-Harithy et al | 2010 | KSA     | CRC         | PCR–RFLP          | 60    | 60       | 11    | 33       | 16        | 0.013    | 7        |
| Al-Harithy et al | 2014 | KSA     | CRC         | PCR–RFLP          | 60    | 60       | 12    | 33       | 16        | 0.013    | 8        |
| Duzkoay et al    | 2015 | Turkey  | CRC         | PCR–RFLP          | 123   | 79       | 9     | 61       | 12        | 0.772    | 7        |
| Mahmoudi et al   | 2014 | Iran    | CRC         | PCR–RFLP          | 197   | 217      | 76    | 83       | 76        | 0.002    | 8        |
| Pechlivanis et al| 2009 | Czech Republic | CRC | PCR–RFLP | 642   | 714      | 63    | 262      | 56        | 0.230    | 6        |
| Wågsater et al   | 2008 | Sweden  | CRC         | TaqMan            | 248   | 256      | 26    | 95       | 16        | 0.563    | 7        |
| Kohan et al      | 2017 | Iran    | BC          | PCR–RFLP          | 150   | 150      | 37    | 63       | 24        | 0.225    | 7        |
| Munoz-Palomeque et al | 2018 | Mexico  | BC          | PCR–RFLP          | 100   | 308      | 5     | 42       | 7         | 0.144    | 8        |
| Wang et al       | 2020 | China   | BC          | TaqMan            | 515   | 541      | 96    | 205      | 76        | 0.390    | 8        |
| **Total**        |      |         |             |                   | 2095  | 2385     | 335   | 877      | 1151      |           |          |

| Study ID         | Year | Country | Cancer type | Genotyping method | Cases | Controls | Cases | Controls | NOS score |
|------------------|------|---------|-------------|-------------------|-------|----------|-------|----------|-----------|
|                  |      |         |             |                   | AA    | GA       | GG    | AA       |           |
| **RETN rs3745367** |      |         |             |                   |       |          |       |          |           |
| Al-Harithy et al | 2014 | KSA     | CRC         | PCR–RFLP          | 60    | 60       | 6     | 51       | 6         | 0.011    | 7        |
| Mahmoudi et al   | 2016 | Iran    | CRC         | PCR–RFLP          | 172   | 190      | 35    | 72       | 26        | 0.768    | 8        |
| Wang et al       | 2020 | China   | BC          | TaqMan            | 515   | 541      | 72    | 259      | 77        | 0.879    | 7        |
| **Total**        |      |         |             |                   | 747   | 791      | 113   | 382      | 109       |           |          |

BC, breast cancer; CRC, colorectal cancer; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa Scale
(0.041) showed significant heterogeneity (Table 4). Sensitivity analysis for detecting the link of RETN rs1862513 and rs3745367 polymorphisms with CRC and BC suggests the reliability and stability of our analysis, as shown in Additional file 1: Fig. S1.
Resistin, an adipocytokine secreted by monocytes and macrophages, has been extensively studied due to its numerous roles in different physiological and pathological processes. It has been found that resistin is associated with inflammatory, metabolic, autoimmune processes in the human body as well as several cancers, including colorectal, breast, lung, endometrial, gastric, pancreatic, and liver cancers [53, 56, 57]. Again, RETN gene, which encodes resistin, has also been investigated for its role in

**Discussion**

Resistin, an adipocytokine secreted by monocytes and macrophages, has been extensively studied due to its numerous roles in different physiological and pathological processes. It has been found that resistin is associated with inflammatory, metabolic, autoimmune processes in the human body as well as several cancers, including colorectal, breast, lung, endometrial, gastric, pancreatic, and liver cancers [53, 56, 57]. Again, RETN gene, which encodes resistin, has also been investigated for its role in

**Fig. 3** Forest plot for detecting the association of resistin with breast cancer in A overall (premenopausal and postmenopausal), B premenopausal women, C postmenopausal women
different diseases, including CRC and BC. Two common SNPs in RETN gene, namely, rs1862513 and rs3745367, have been evaluated for the risk link with BC and CRC [18, 21–23]. This combined meta-analytic approach summarized that serum and plasma resistin levels are positively connected with an increased risk of CRC and BC. Again, \textit{RETN} rs1862513 is also linked with the risk of CRC. Regardless of the inconsistent outcomes of the previous analyses, this is the first study evaluating the relationship of resistin levels and \textit{RETN} gene polymorphisms at a time in both BC and CRC patients.

Accumulating evidence suggests that there is a significant correlation between attenuation in circulatory resistin levels and different diseases. It has been proposed that resistin plays a key role in cancer progression and cell cycle regulation. Resistin also has a potential link between inflammation, atherosclerosis, obesity, cardiovascular pathology, non-alcoholic fatty liver disease, and rheumatic diseases [34, 48]. Studies revealed that circulating resistin could promote several processes, including metastasis, proliferation, and angiogenesis associated with cancer development through stimulating different signaling mechanisms such as p38 MAPK/ NF-κB and PI3K/Akt pathways [58]. Although multiple studies with resistin found that higher resistin levels are linked to an increased risk of carcinogenesis, a few studies found no or an insignificant association.

The connection of resistin with CRC risk has been studied extensively in a wide variety of populations. The potential effect of resistin in CRC can be elucidated via different mechanisms. Several in vitro studies have demonstrated that the increased levels of resistin have proinflammatory effects controlled by the stimulation of TLR4 receptor and NF-κB signaling pathways. Besides, some studies also reported that resistin regulates matrix metalloproteinases (MMPs) production and modulates vascular endothelial growth factor (VEGF) secretion, which is linked with tumor invasiveness [4]. We found that high

**Table 4 Meta-analysis and subgroup analysis of selected studies evaluating the association of \textit{RETN} gene polymorphisms with colorectal and breast cancer**

| Genetic model | Test of association | Test of heterogeneity | Publication bias (p-value) |
|---------------|---------------------|-----------------------|---------------------------|
|               | OR 95% CI p-value   | Model p-value I² (%)  | Egger’s test Begg–Mazumdar’s test |
| \textit{RETN} rs1862513 (CRC) |                   |                       |                           |
| Codominant 1 (GC vs. CC) | 1.24 1.05–1.47 0.010 | Fixed 0.165 36.28 0.226 | 0.091 |
| Codominant 2 (GG vs. CC) | 1.31 1.08–1.69 0.036 | Fixed 0.292 18.74 0.236 | 0.348 |
| Dominant model (GG+GC vs. CC) | 1.25 1.07–1.46 0.005 | Fixed 0.418 0 0.526 | 0.188 |
| Recessive model (GG vs. GC+CC) | 1.01 0.72–1.43 0.934 | Random 0.095 46.74 0.120 | 0.039 |
| Over dominant (GC vs. GG+CC) | 1.25 0.98–1.60 0.070 | Random 0.097 46.37 0.168 | 0.060 |
| Allele contrast (G vs. C) | 1.16 1.03–1.30 0.012 | Fixed 0.541 0 0.297 | 0.091 |
| \textit{RETN} rs1862513 (BC) |                   |                       |                           |
| Codominant 1 (GC vs. CC) | 1.05 0.86–1.30 0.622 | Fixed 0.101 56.43 0.244 | 0.602 |
| Codominant 2 (GG vs. CC) | 1.51 1.12–2.03 0.007 | Fixed 0.360 2.23 0.166 | 0.117 |
| Dominant model (GG+GC vs. CC) | 1.16 0.95–1.41 0.135 | Fixed 0.109 54.89 0.124 | 0.602 |
| Recessive model (GG vs. GC+CC) | 1.51 1.15–1.99 0.004 | Fixed 0.653 0 0.125 | 0.117 |
| Over dominant (GC vs. GG+CC) | 1.02 0.73–1.43 0.912 | Random 0.095 57.48 0.346 | 0.117 |
| Allele contrast (G vs. C) | 1.21 1.05–1.40 0.008 | Fixed 0.172 43.23 0.033 | 0.117 |
| \textit{RETN} rs3745367 (CRC+BC) |                   |                       |                           |
| Codominant 1 (AG vs. GG) | 1.41 0.80–2.48 0.239 | Random 0.029 71.64 0.436 | 0.602 |
| Codominant 2 (AA vs. GG) | 1.27 0.93–1.74 0.138 | Fixed 0.142 48.71 0.117 | 0.117 |
| Dominant model (AA+AG vs. GG) | 1.04 0.77–1.40 0.794 | Fixed 0.245 28.99 0.890 | 0.602 |
| Recessive model (AA vs. AG+GG) | 1.42 0.85–2.36 0.182 | Random 0.041 68.78 0.287 | 0.117 |
| Over dominant (AG vs. AA+GG) | 1.12 0.84–1.49 0.443 | Fixed 0.324 11.32 0.786 | 0.602 |
| Allele contrast (A vs. G) | 1.24 0.78–1.98 0.359 | Random 0.041 68.66 0.627 | 0.602 |

Bold values indicate statistically significant (p < 0.05).

BC, breast cancer; CRC, colorectal cancer; OR, odds ratio; 95% CI, 95% confidence interval.
Fig. 4 Forest plot for detecting the association between RETN rs1862513 polymorphism and colorectal cancer
### 1.2.1 GC vs. CC

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 63                  | 115            | 188          | 3.7%   | 1.26 [0.76, 2.10]              |
| Munoz-Palomeque et al 2018 | 42                  | 95             | 137          | 4.1%   | 1.55 [0.97, 2.47]              |
| Wang et al 2020            | 205                 | 419            | 624          | 7.8%   | 0.89 [0.68, 1.16]              |
| Subtotal (95% CI)          | 627                 | 892            | 1524         | 15.6%  | 1.15 [0.80, 1.63]              |

Total events: 310, 408
Heterogeneity: Tau² = 0.06; Chi² = 4.50, df = 2 (P = 0.01); P = 56%
Test for overall effect: Z = 0.75 (P = 0.45)

### 1.2.2 GG vs. CC

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 37                  | 87             | 124          | 2.6%   | 1.94 [1.03, 3.66]              |
| Munoz-Palomeque et al 2018 | 5                   | 58             | 63           | 0.9%   | 2.60 [0.82, 8.79]              |
| Wang et al 2020            | 96                  | 310            | 406          | 5.9%   | 1.32 [0.93, 1.88]              |
| Subtotal (95% CI)          | 455                 | 593            | 1048         | 9.4%   | 1.52 [1.11, 2.06]              |

Total events: 139, 107
Heterogeneity: Tau² = 0.00; Chi² = 2.05, df = 2 (P = 0.36); P = 2%
Test for overall effect: Z = 2.64 (P = 0.008)

### 1.2.3 GG vs. GC

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 37                  | 100            | 137          | 2.7%   | 1.54 [0.83, 2.87]              |
| Munoz-Palomeque et al 2018 | 5                   | 47             | 52           | 0.9%   | 1.73 [0.52, 5.77]              |
| Wang et al 2020            | 96                  | 301            | 397          | 5.9%   | 1.48 [1.04, 2.12]              |
| Subtotal (95% CI)          | 448                 | 513            | 961          | 9.4%   | 1.51 [1.12, 2.04]              |

Total events: 138, 107
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.87); P = 0%
Test for overall effect: Z = 2.72 (P = 0.007)

### 1.2.4 Dominant Model (GG+GC vs. CC)

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 100                 | 150            | 250          | 4.1%   | 1.45 [0.91, 2.32]              |
| Munoz-Palomeque et al 2018 | 47                  | 100            | 147          | 4.3%   | 1.62 [1.03, 2.58]              |
| Wang et al 2020            | 301                 | 515            | 816          | 8.2%   | 0.99 [0.78, 1.27]              |
| Subtotal (95% CI)          | 765                 | 999            | 1764         | 16.6%  | 1.26 [0.91, 1.75]              |

Total events: 448, 513
Heterogeneity: Tau² = 0.05; Chi² = 4.43, df = 2 (P = 0.011); P = 95%
Test for overall effect: Z = 1.38 (P = 0.17)

### 1.2.5 Recessive model (GG vs. GC+CC)

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 37                  | 150            | 187          | 3.1%   | 1.72 [0.97, 3.05]              |
| Munoz-Palomeque et al 2018 | 5                   | 100            | 105          | 0.9%   | 2.26 [0.70, 7.30]              |
| Wang et al 2020            | 96                  | 515            | 611          | 6.3%   | 1.40 [1.01, 1.95]              |
| Subtotal (95% CI)          | 765                 | 999            | 1764         | 10.3%  | 1.51 [1.14, 1.99]              |

Total events: 138, 107
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.65); P = 0%
Test for overall effect: Z = 2.92 (P = 0.004)

### 1.2.6 Overdominant model (GC vs. GG+CC)

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 63                  | 150            | 213          | 4.3%   | 1.00 [0.63, 1.58]              |
| Munoz-Palomeque et al 2018 | 42                  | 100            | 142          | 4.2%   | 1.46 [0.92, 2.32]              |
| Wang et al 2020            | 205                 | 515            | 720          | 8.2%   | 0.92 [0.64, 1.35]              |
| Subtotal (95% CI)          | 765                 | 999            | 1764         | 16.7%  | 1.02 [0.73, 1.43]              |

Total events: 310, 406
Heterogeneity: Tau² = 0.05; Chi² = 4.70, df = 2 (P = 0.011); P = 57%
Test for overall effect: Z = 2.92 (P = 0.004)

### 1.2.7 Allele Contrast (G Vs. C)

| Study or Subgroup          | Experimental Events | Control Events | Total Events | Weight | Odds Ratio M-H, Random, 95% CI |
|----------------------------|---------------------|----------------|--------------|--------|-------------------------------|
| Kohan et al 2017           | 137                 | 300            | 437          | 6.4%   | 1.43 [1.03, 1.98]              |
| Munoz-Palomeque et al 2018 | 52                  | 200            | 252          | 5.5%   | 1.51 [1.04, 2.20]              |
| Wang et al 2020            | 397                 | 1030           | 1427         | 10.0%  | 1.10 [0.92, 1.31]              |
| Subtotal (95% CI)          | 1530                | 1998           | 3528         | 21.9%  | 1.27 [1.03, 1.58]              |

Total events: 598, 620
Heterogeneity: Tau² = 0.02; Chi² = 3.52, df = 2 (P = 0.17); P = 43%
Test for overall effect: Z = 2.19 (P = 0.03)

Total (95% CI): 5355, 6993; 100.0%; 1.27 [1.13, 1.42]

Fig. 5 Forest plot for detecting the association between RETN rs1862513 polymorphism and breast cancer.
### Fig. 6

Forest plot for detecting the association of RETN rs3745367 polymorphisms with colorectal and breast cancer

| Study or Subgroup | 2.1.1 AG vs. GG | 2.1.2 AA vs. GG | 2.1.3 AA vs. AG | 2.1.4 Dominant model (AA*AG vs. GG) | 2.1.5 Recessive model (AA vs. AG+GG) | 2.1.6 Over-dominant model (AG vs. AA+GG) | 2.1.7 Allele contrast (A Vs. G) |
|-------------------|-----------------|-----------------|-----------------|-----------------------------------|------------------------------------|-----------------------------------|-----------------|
|                   | Events | Total | Events | Total | Weight | Odds Ratio | M-H, Fixed, 95% CI |
| Alharthy et al 2014 | 51     | 54     | 39     | 54     | 0.2%   | 6.54 [0.77, 24.18] |
| Mahmoudi et al 2016 | 72     | 137    | 86     | 164    | 3.5%   | 1.00 [0.64, 1.59]  |
| Wang et al 2020    | 259    | 443    | 252    | 464    | 9.7%   | 1.18 [0.91, 1.54]  |
| Subtotal (95% CI)  | 634    | 1682   | 682    | 134%   | 1.22 [0.96, 1.52]  |
| Total events       | 382    | 377    | 109    |        |         |                   |
| Heterogeneity: Chi² = 7.08, df = 2 (P = 0.03); I² = 72% |
| Test for overall effect Z = 1.75 (P = 0.08) |

| Alharthy et al 2014 | 6     | 9     | 6     | 21    | 0.1%   | 5.00 [0.93, 26.79] |
| Mahmoudi et al 2016 | 35    | 100   | 26    | 104   | 1.6%   | 1.62 [0.86, 2.96]  |
| Wang et al 2020     | 72    | 256   | 77    | 289   | 4.9%   | 1.08 [0.74, 1.57]  |
| Subtotal (95% CI)   | 365   | 414   | 66    | 134%   | 1.27 [0.93, 1.74]  |
| Total events        | 113   | 109   |        |        |         |                   |
| Heterogeneity: Chi² = 3.90, df = 2 (P = 0.14); I² = 49% |
| Test for overall effect Z = 1.51 (P = 0.13) |

| Alharthy et al 2014 | 6     | 57    | 6     | 45    | 0.8%   | 0.76 [0.23, 2.55]  |
| Mahmoudi et al 2016 | 35    | 107   | 26    | 112   | 1.8%   | 1.61 [0.89, 2.92]  |
| Wang et al 2020     | 72    | 331   | 77    | 329   | 5.7%   | 0.91 [0.63, 1.31]  |
| Subtotal (95% CI)   | 495   | 486   | 79    | 14%    | 1.04 [0.77, 1.41]  |
| Total events        | 113   | 109   |        |        |         |                   |
| Heterogeneity: Chi² = 2.82, df = 2 (P = 0.24); I² = 29% |
| Test for overall effect Z = 0.27 (P = 0.79) |

| Alharthy et al 2014 | 57    | 60    | 45    | 60    | 0.2%   | 0.33 [0.13, 0.82]  |
| Mahmoudi et al 2016 | 107   | 172   | 112   | 190   | 3.8%   | 1.15 [0.75, 1.75]  |
| Wang et al 2020     | 321   | 515   | 220   | 541   | 10.8%  | 1.16 [0.90, 1.50]  |
| Subtotal (95% CI)   | 747   | 791   | 14%   | 1.23 [1.00, 1.52] |
| Total events        | 495   | 486   |        |        |         |                   |
| Heterogeneity: Chi² = 6.43, df = 2 (P = 0.04); I² = 69% |
| Test for overall effect Z = 1.93 (P = 0.05) |

| Alharthy et al 2010 | 6     | 60    | 6     | 60    | 0.5%   | 1.00 [0.30, 3.30]  |
| Mahmoudi et al 2016 | 35    | 172   | 26    | 190   | 1.9%   | 1.61 [0.92, 2.81]  |
| Wang et al 2020     | 72    | 515   | 77    | 541   | 8.1%   | 0.99 [0.69, 1.39]  |
| Subtotal (95% CI)   | 747   | 791   | 8.5%  | 1.12 [0.84, 1.49] |
| Total events        | 113   | 109   |        |        |         |                   |
| Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² = 11% |
| Test for overall effect Z = 0.78 (P = 0.44) |

| Alharthy et al 2014 | 51    | 60    | 39    | 60    | 0.6%   | 3.05 [1.26, 7.39]  |
| Mahmoudi et al 2016 | 72    | 172   | 86    | 190   | 4.5%   | 0.87 [0.57, 1.32]  |
| Wang et al 2020     | 259   | 515   | 252   | 541   | 11.5%  | 1.16 [0.91, 1.48]  |
| Subtotal (95% CI)   | 747   | 791   | 16%   | 1.14 [0.94, 1.46] |
| Total events        | 382   | 377   |        |        |         |                   |
| Heterogeneity: Chi² = 6.38, df = 2 (P = 0.04); I² = 69% |
| Test for overall effect Z = 1.31 (P = 0.19) |

| Alharthy et al 2014 | 63    | 120   | 51    | 120   | 2.3%   | 1.50 [0.90, 2.49]  |
| Mahmoudi et al 2016 | 142   | 344   | 138   | 380   | 7.3%   | 1.23 [0.91, 1.68]  |
| Wang et al 2020     | 403   | 1030  | 406   | 1082  | 22.8%  | 1.07 [0.80, 1.42]  |
| Subtotal (95% CI)   | 1494  | 1582  | 32.3% | 1.14 [0.98, 1.31] |
| Total events        | 608   | 595   |        |        |         |                   |
| Heterogeneity: Chi² = 1.85, df = 2 (P = 0.40); I² = 0% |
| Test for overall effect Z = 1.73 (P = 0.08) |

| Alharthy et al 2014 | 5229  | 5537  | 100%  | 1.16 [1.07, 1.26] |
| Mahmoudi et al 2016 | 2206  | 2162  |        |        |                   |
| Wang et al 2020     | 5229  | 5537  |        |        |                   |
| Heterogeneity: Chi² = 31.87, df = 20 (P = 0.04); I² = 37% |
| Test for overall effect Z = 3.61 (P = 0.0003) |
| Test for subarous differences: Chi² = 1.46, df = 6 (P = 0.96), I² = 0% |
resistin levels are associated with CRC. According to our findings, patients with CRC have significantly higher resistin concentration than that of the control group (MD = 3.39). Our analysis is consistent with the previous findings in different populations, including population from the Kingdom of Saudi Arabia [25], Italy [26], Turkey [27, 29, 33], South Korea [28], Poland [30], China [31, 39],

Fig. 7 Funnel plot for detecting the association of resistin in A colorectal cancer, B breast cancer
Fig. 8 Funnel plots for detecting the association of RETN rs1862513 and rs3745367 polymorphisms with colorectal and breast cancer
CRC patients compared to healthy controls (MD population. We found an elevated plasma resistin level in Korean [28], Polish [30], Chinese [31], and Egyptian [32] populations. In our study, the meta-analysis of RETN polymorphisms with CRC and BC, on the other hand, found no statistically significant risk association in any genetic model. Our results are in conformance with the previous results [19]. However, no association with CRC was observed in some previous studies [11, 21, 25, 38]. Again, rs1862513 polymorphism in BC also showed a significantly strong correlation in codominant 2 (OR 1.51), codominant 3 (OR 1.51), recessive (OR 1.51), and allele (OR 1.21) models. Muñoz-Palomeque et al. [18] also showed a significantly increased risk of BC with this SNP. However, no statistically strong correlation was observed in previous analysis by Wang et al. [22].

The meta-analysis of the RETN rs3745367 polymorphism in CRC and BC, on the other hand, found no statistically significant risk association in any genetic model. Our results are consistent with those of Wang et al. [22] in BC, Mahmoudi et al. [23] in CRC. However, Alharithy et al. [24]...
et al. [24] showed a significantly increased association of rs3745367 variant with the risk of CRC.

We should point out some limitations of our meta-analysis. Firstly, although we have followed a perfect strategy for literature search, there might be a possibility of missing some eligible studies. Furthermore, we only included studies that were published in English. Secondly, there appeared some sort of publication bias. Thirdly, we found significant heterogeneity across the studies. Study design, quality, and sample type may account for this heterogeneity. Fourthly, present meta-analyses are based on case–control studies, and the inherent lacking's of which may influence our outcomes to some extent. Finally, we could not discuss some potential confounders that may be associated with the alteration of resistin levels and RETN polymorphisms such as obesity, smoking, dietary habits, sex, alcohol, lack of exercise, and clinicopathological characteristics, including tumor stage, distant metastasis, and type of cancers. However, keeping in mind the potential role of circulating resistin and RETN genetic polymorphisms in both CRC and BC risk and the inconsistent published evidence based on the effect of resistin, the present study is the first combined effort with both cancers and is of greater importance.

**Conclusion**

In conclusion, the present study indicates that serum and plasma resistin levels are positively associated with an elevated risk of CRC. Besides, elevated resistin level is positively associated with increased BC risk in premenopausal and postmenopausal women. Moreover, RETN rs1862513 polymorphism is connected with the risk of both CRC and BC. Our analysis will help enhance the understanding of cancer risks with resistin levels and RETN genetic variants. However, based on the limitations mentioned above, more randomized trials with a larger sample size are required to confirm the relationship of resistin and RETN polymorphisms with the development of CRC and BC.

**Methods**

**Literature search**

Both meta-analyses were carried out following the guidelines of PRISMA [61]. For collecting data of resistin, a comprehensive literature search was conducted in PubMed, ScienceDirect, BMC, EMBASE, Cochrane Library, Web of Science, and Google Scholar databases using the following search keywords: “resistin,” “adipokines,” “adipocytokines,” “serum resistin,” “plasma resistin,” “resistin and colorectal cancer,” “resistin and breast cancer.” Again, for RETN genetic polymorphisms-related data, we searched on the same databases using the following keywords: “resistin,” “RETN,” “SNPs,” “polymorphisms,” “variants,” “rs1862513,” or “C-180G,” or “C-420G,” “rs3745367,” or “G + 299A,” “RETN and colorectal cancer,” “RETN and breast cancer.” In addition, we manually reviewed the list of bibliography from the retrieved articles to include relevant studies. Furthermore, we have added literature only written in English.

**Study selection criteria**

The following criteria were used to select studies for inclusion in both meta-analyses: (1) If the study evaluated the link of resistin level and RETN polymorphisms (rs1862513 and/or 3745367) with BC and CRC; (2) if it was a case–control, cross-sectional, or cohort study; (3) if the study provided appropriate data to calculate resistin level and in case of genetic meta-analysis if the studies provided useful genotypic data; and (4) if the study performed on human. Studies were excluded if they had the following criteria: (1) If the study was a review, editorial, or letter to the editor; (2) if there is no control cohort; (3) if the study had inadequate data; and (4) if the authors with incomplete study data did not reply to the requests from the authors.

**Data extraction**

Two authors (MAA and TA) independently assessed the eligibility of included studies and any disagreements were resolved by consensus with another author (MSI). From each article selected, we retrieved the following information: first author’s name, publication year, study conducting country, cancer type, sources of the sample (plasma or serum) or SNP studied, type of sample, number of study cases and controls, assay type or genotyping method, name of the kit provider, mean resistin level (ng/ml) ± standard deviation (SD) in both cases and controls, and p-value of HWE of controls for genetic association study. Where median and range or interquartile range were given for resistin level, we calculated mean and SD using the method described by Wan et al. [62].

**Quality score assessment**

The quality of each selected study for our meta-analyses involving the correlation of serum or plasma resistin levels or the association of RETN polymorphisms in CRC and BC was assessed based on the Newcastle–Ottawa Scale (NOS) [63]. We evaluated the quality of each study following three aspects: (1) the study selection procedure, (2) literature comparability, and (3) the exposure determination in case–control studies. NOS total scores ranged from 0 to 9, with a score greater than 7 indicating a high-quality study.
Statistical analysis
All statistical analysis was performed using the Review Manager (RevMan) 5.4 software (Nordic Cochrane Center, Copenhagen, Denmark). We calculated all data as mean (ng/ml) ± SD to assess plasma or serum resistin relationship with CRC and BC. Again, for genetic association analysis, we calculated the association of RETN variants in seven genetic models, including codominant 1–3, dominant, overdominant, recessive, and allele model. The Q-statistic to test the heterogeneity between studies and the I²-statistic to quantify the total differences resulting from heterogeneity was calculated. We selected the random effect model for calculating the pooled mean differences when p < 0.50%. Our meta-analyses also assessed potential publication bias by applying Egger’s regression test [64] and Begg’s rank correlation test [65]. We stratified all collected data according to the menopausal status of subjects (pre-menopausal and postmenopausal) in BC and sources of the sample (serum or plasma) in CRC and employed in subgroup analyses (forest plot) to evaluate the source of heterogeneity for evaluating the association of resistin level. In all analyses, p < 0.05 was considered to be statistically significant.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s43042-022-00240-w.

Additional file 1. Supplementary material: Sensitivity analysis.

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