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Association of Obesity with the Occurrence of Gastrointestinal Cancer- A Meta-Analysis

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ABSTRACT: *Obesity is a risk factor for many diseases especially cancer. Numerous studies have been performed to examine the relation between obesity and different types of gastrointestinal cancer. However, involvement of obesity in overall gastrointestinal cancer risk is not very clear. Therefore, a meta-analysis was performed to investigate the association of obesity and overall gastrointestinal cancer risk. A thorough systematic search were performed on PubMed, MEDLINE and other databases and relevant studies were identified and scrutinised. A random effect model was used to calculate the correlation using risk ratio (RR) at 95% confidence interval. Publication bias was assessed by funnel plots. A total of 56 studies were used to perform meta-analysis. The pooled risk ratio calculated showed a significant relation between obesity and gastrointestinal cancer risk (RR = 1.742, 95% CI =1.54 - 1.96, P< 0.001). Subgroup analysis was also performed for different types of gastrointestinal cancer such as oesophageal cancer, stomach cancer, liver cancer, pancreatic cancer, and colorectal cancer. The pooled risk ratio for each type of gastrointestinal cancer was found to be RR = 2.376 (oesophageal cancer), RR = 1.131 (stomach cancer), RR = 1.976 (liver cancer), RR = 1.474 (pancreatic cancer), and RR = 1.428 (colorectal cancer). There was observed no significant bias in the study. This study suggested that obesity is significantly associated with risk of gastrointestinal cancer especially oesophageal cancer. However, further investigations and large clinical trials are required to make an impactful and conclusive statement about this association.*

Keywords: *Obesity; risk ratio; gastrointestinal cancers; Oesophageal cancer; meta-analysis*

INTRODUCTION

Gastrointestinal cancer is the cancer of gastrointestinal track particularly of oesophagus, stomach, small and large intestine, colon, rectum and related organs as liver, pancreas, and gallbladder (Klint et al., 2010, Siegel RL et al., 2017). This cancer like other cancer types shows poor prognosis and is often detected when it has reached to the advanced stages (Arnold et al., 2020).

The prevalence of gastrointestinal cancer vary among different populations due to significant geographical variations. For example, China alone shares 54% of the global burden of oesophagus squamous cell carcinoma (OSCC), a type of oesophageal cancer. It is found that the gastrointestinal cancer is more prevalent in the developed countries like United States, Japan, China etc (Prasad and Tyagi, 2015). According to statistics, it accounts for 18.7% of global cancer incidence and mortality rates of 22.6% in 2020 (YumoXie et al., 2021) and is more common among men as compared to women. The common risk factors of gastrointestinal cancer includes infections, smoking, fatty diet, alcohol consumption, age, gender, race, family history, and the area of prevalence (Arnold et al., 2020; Ilic and Ilic, 2002).

According to WHO, obesity is defined as the excessive accumulation of fat in the body which necessarily can affect the normal health status and is determined by body mass index (BMI). Obesity is common due to the modernization and economic stability in the world which ensures the availability of affordable and excess food to everyone and physical inactivity (Ng et al., 2012). Furthermore, it is not age restricted and is present everywhere regardless of geography, ethnicity, and economic status (Chooi et al., 2019). Obesity presents different physiological problems and contribute to the development of several diseases particularly different types of gastrointestinal cancer (Blüher, 2019; Krupa-Kotara and Dakowska, 2021). World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) in 2018 issued a Continuous Update Project (CUP), a joint review indicating that there is mounting evidence that creates a nexus between obesity and esophagus adenocarcinoma, pancreatic, liver, colorectal and kidney cancer.

Various studies have been performed to observe the relation between obesity and different types of

gastrointestinal cancer, but few showed a pooled effect. These studies showed diverse results making it difficult to present a statement about role of obesity in gastrointestinal cancer risk. Therefore, this meta-analysis was performed to elucidate the association between obesity and occurrence of gastrointestinal cancer.

METHODS

a- Literature Search Strategy

Various search engines like PubMed, MEDLINE and others were searched for studies showing the association between obesity and gastrointestinal cancer. Studies were also included from the citations in the selected papers and review articles. The key words for these searches included 'obesity and risk of Gastrointestinal cancer', 'BMI and risk of Gastrointestinal cancer', 'overweight and risk of Gastrointestinal cancer', 'obesity and risk of esophageal cancer', 'obesity and risk of gastric cancer', 'obesity and risk of stomach cancer', 'obesity and risk of pancreatic cancer', 'obesity and risk of liver cancer', 'obesity and risk of colorectal cancer', 'obesity and risk of gallbladder cancer'.

b- Selection Criteria:

Those published studies were included in our meta-analysis which met the following criteria: (1) studies had to be cohort or case–control study in which gastrointestinal cancer (esophageal, stomach, liver, pancreatic, colorectal) incidence or mortality was taken as outcome; (2) the exposure included overweight and/or obesity defined by body mass index (BMI) (the weight in kilograms divided by the square of height in meters), (3) estimates of relative risk (hazard ratio, odds ratio) and relative risk (RR) for at least 3 categories of BMI were reported in studies.

c- Literature Retrieval and Data Extraction:

Initially, 135 studies were chosen through search of different databases. Out of these, 73 studies were excluded from further evaluation because their abstract did not contain the required information for our data. Remaining 62 studies were evaluated for full text assessment. Out of these further 6 studies were excluded due to missing data. Finally, 56 studies were found eligible for performing meta-analysis and required data was extracted from these studies.

From each study, the following information was extracted: Author's name, publication year, country where study was performed; study design (cohort or case–control), sample size,

age range of participants, number of patients, categories of body mass index, relative risk for each category of body mass index, gender, type of Gastrointestinal cancer, outcome as yes or no, estimated relative risk with 95% Cl. The adjusted relative risks were noted where available.

d- Exposure definition

BMI ranges as specified by the WHO was used i.e. 18.5 to 24.9kg/m^2 range represents the normal BMI, whereas BMI greater than 25 kg/m 2 represents overweight persons and a BMI greater than 30 kg/m^2 represent obese. If BMI exceeds 40 kg/m^2,it is classified as severe obesity (Chooi et al., 2019).

e- Statistical Analysis

Random effect model was used to calculate the summary or pooled risk ratio (RR) estimate with 95% Cls. Some studies represented results in the form of hazard ratio (HR) and odd ratio (OR), but these association measures were considered as risk ratio in our study. There were studies like Calle et al, 2003, and others which published RR for obesity group (>30 kg/m) in more than one category such as a risk ratio estimate for 30 to 35 kg/m^2 in one category, another risk estimate for 35 to 40 kg/m^2 categorised as obese II or severe obese and so on. For these a mean of all the relative risk estimates was taken and used in the meta-analysis. Also, some papers published RR separately for male and female, for these again a mean risk ratio was taken. Most adjusted risk ratio value was taken. The assessment of heterogeneity in the selected studies was done by using Q and I^2 statistics. Publication bias was assessed using funnel plot. All analyses were performed using the Comprehensive Meta Analysis (CMA) Version 3.0.

RESULTS

a- Literature retrieval and Characteristics of included Studies:

After thoroughly analyzing 135 studies finally 56 studies were selected for performing meta-analysis (Figure 1). The studies included in the meta-analysis were published between 1995 and 2018 and contain both cohort and case control studies. It was observed that these studies were performed in almost every region of the world including US, England, Netherlands, Australia, Sweden, Israel, Singapore, Norway, Japan, China, Australia, Korea, Italy, Canada, Ireland, and South Korea and all studies included in the meta-analysis had been seen to report result on only one of different types of

gastrointestinal cancer (oesophagus cancer, gastric cancer, liver cancer, pancreatic cancer, and colorectal cancer) but some studies like (Pan et al., 2003; Jee et al., 2008; Batty et al., 2005) reported for every type of gastrointestinal cancer. So, for these studies we have entered entries for each cancer type separately. Also, most studies used Cox regression model and Cox proportional hazard model to find relative risk (RR) between obesity and different type of gastrointestinal cancer. Other main characteristics of the selected studies were shown in table 1.

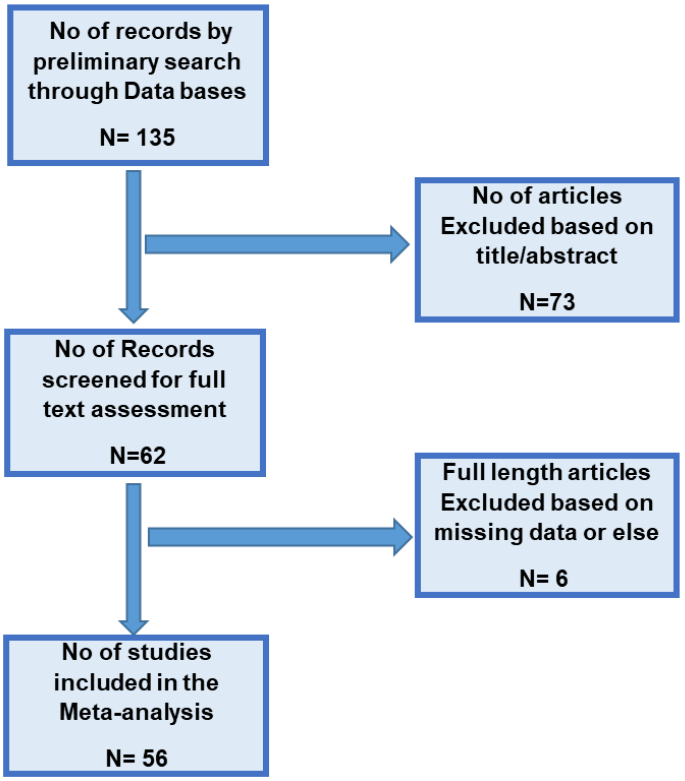


Fig. 1: Flowchart representing the steps of the literature search

Table 1: Characteristics of the Eligible studies

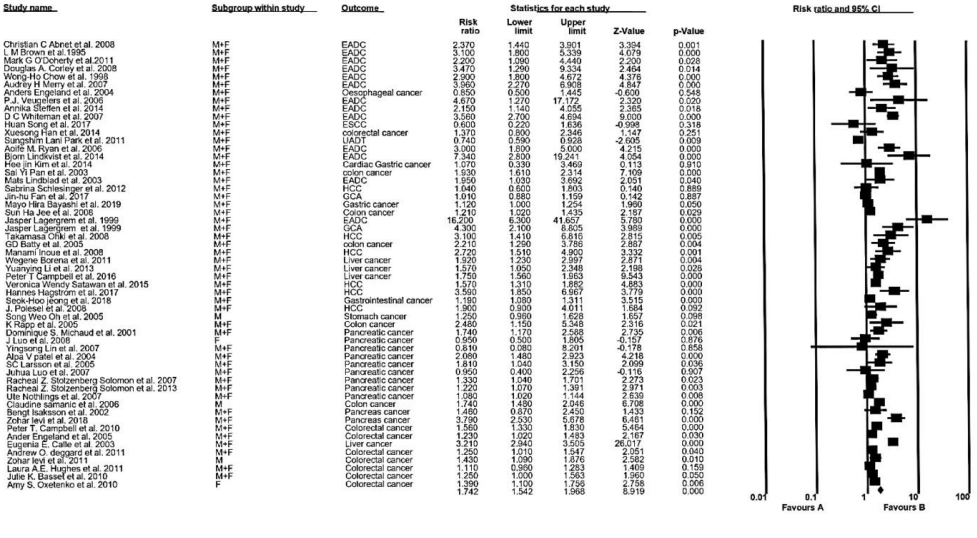
	Study		No. of participants		Type of study	No. of patients with BMI				Gender	Type of GIT cancer	Age	Geo Location	RR
	Author	Year	Control	Patients		Under	Normal	Over	Obese					
1	Abnet et al.	2008	480,475	371	Cohort	2 (1.61)	71 (1.00)	194 (1.65)	104 (2.09)	M+F	EADC	50-71	USA	2.37 (1.44–3.59)
2	Brown et al.	1995	750	174	Case control	24 (1.00)	31 (1.1)	27 (1.2)	79 (3.1)	M	EADC	30-79	USA	3.1 (1.8-5.3)
3	O'Doherty et al.	2011	218854	253	Cohort	0	59 (1.00)	119 (1.3)	75 (2.20)	M+F	EADC	50-71	USA	2.20 (1.09 to 4.09)
4	Corley et al.	2008	206974	101	Nested Case-control	8 (1.00)	25 (2.09)	22 (3.47)	?	M+F	EADC	?	USA	3.47 (1.29-9.33)
5	Chow et al.	1998	695	554	Case-control	45 (1.00)	63 (1.3)	85 (2.00)	99 (2.90)	M+F	EADC	30-79	USA	2.90 (1.8–4.7)
6	Merry et al.	2007	120852	133	Cohort	3 (1.29)	51 (1)	60 (1.40)	19 (3.96)	M+F	EADC	55-69	Nether land	3.96 (2.27 to 6.88)
7	Engeland et al.	2004	2 million	2245	Cohort	40 (2.46)	1208 (1.00)	827 (0.82)	170 (0.85)	M+F	Oesophag-eal cancer	20-74	Norway	0.85 (0.50–0.82)
8	Veugelers et al.	2006	102	57	Case-control	0	16% (1.00)	43% (1.58)	41% (4.67)	M+F	EADC	?	Canada	4.67 (1.27–17.19)
9	Steffen et al.	2014	395456	124	Cohort	37 (1.15)	24 (1.36)	30 (1.76)	33 (2.15)	M+F	EADC	20-70	UK	2.15 (1.14–4.05)
10	Whiteman et al.	2007	1580	801	Case-control	1 (0.5)	71 (1.00)	150 (1.2)	130 (3.56)	M+F	EADC	18-79	Australia	3.56 (2.7 to 13.6)
11	Song et al.	2017	96331	342	cohort	12 (0.87)	274 (1.00)	52 (0.57)	4 (0.60)	M+F	ESCC	40-69	Japan	0.60 (0.22–1.61)
12	Han et al.	2014	13901	298	Cohort	13 (0.87)	210 (1.00)	58 (1.07)	17 (1.37)	M	Colorectal	45-64	USA	1.37 (0.8-3.11)
13	Park et al.	2011	2173	2048	Case-control	57 (2.10)	785 (1.00)	613 (0.74)	252 (0.74)	M+F	UADT	?	Europe	0.74 (0.59 - 0.93)
14	Ryan et al.	2006	893	283	Case-control	40 (1.00)	43 (1.00)	74 (1.9)	131 (3.00)	M+F	EADC	?	Ireland	3.0 (1.8–5.0)
15	Lindkvist et al.	2014	578700	114	Cohort	5 (1.00)	36 (3.27)	31 (5.19)	42 (7.34)	M+F	EADC	?	Australia Norway Sweden	7.34 (2.8–18.68)
16	Kim et al.	2014	1288	998	Case-control	468 (1.00)	266 (1.08)	244 (1.22)	26 (1.07)	M+F	Cardiac Gastric	30-80	South Korea	1.07 (0.331–2.255)
17	Pan et al.	2003	5039	1176	Case-control	?	?	1176 (0.97)	1176 (1.25)	M+F	Stomach	20-76	Canada	1.25 (1.03, 1.51)
				1722		?	?	1722 (1.4)	1722 (1.93)		Colon	20-76		1.93 (1.61, 2.31)
				1447		?	?	1447 (1.36)	1447 1.65		Rectum	20-76		1.65 (1.36, 2.00)
				630		?	?	630 0.99	630 (1.51)		Pancreatic	20-76		1.51 (1.19, 1.92)
				309		?	?	309 (0.89)	309 (1.17)		Liver	20-76		1.17 (0.83, 1.66)
18	Lindblad et al.	2003	10,000	287	Case-control	8 (1.29)	49 (1.00)	94 (1.47)	36 (1.95)	M+F	EADC	40-84	Sweden	1.95 (1.03–3.02)
19	Schlesinger et al.	2012	359525	177	Cohort	?	33 (1.00)	49 (0.96)	95 (1.04)	M+F	HCC	?	Europe	1.04 (0.60–1.83)
20	Fan et al.	2017	29446	1716	Cohort	403 (1.00)	442 (1.02)	390 (1.01)	?	M+F	GCA	?	China	1.01 (0.88–1.16)
21	Bayashi et al.	2019	92056	2860	Cohort	145 (1.17)	1988 (1.00)	426 (1.00)	301 (1.12)	M+F	Gastric cancer	40-69	Japan	1.12 (1.00 - 1.51)
22	Jee et al.	2008	1213829	13810	Cohort	2332 (0.95)	11790 (1.01)	4320 (0.98)	242 (1.07)	M+F	Stomach	30-95	Korea	1.07 (1.05–1.64)
				1231		291 (2.11)	1033 (1.12)	265 (1.52)	5 (1.48)		Oesophagus	30-95		1.48 (0.51–11.7)
				4706		612 (0.72)	4100 (0.99)	1791 (1.00)	127 (1.21)		Colon	30-95		1.21 (1.02–1.98)
				7646		1057 (0.87)	6639 (0.92)	2649 (1.09)	175 (1.51)		Liver	30-95		1.51 (1.27–2.10)
				1959		279 (0.87)	1626 (1.02)	705 (1.20)	51 (1.57)		Pancreatic	30-95		1.57 (0.75–2.38)
				2406		367	2021	883	67		Gallbladder	30-95		1.54

						(0.88)	(0.99)	(1.12)	(1.54)					(1.11–2.44)
23	Lagergrem etal.	1999	820	189	Case-control	10 (1.00)	68 (3.20)	89 (6.90)	22 (16.20)	M+F	EADC	<80	Sweden	16.20 (6.3–41.4)
24	Lagergrem et al.	1999	820	262	Case-control	47 (1.00)	100 (1.30)	91 (2.20)	34 (4.30)	M+F	GCA	<80	Sweden	4.30 (2.1–8.7)
25	Ohki et al.	2008	1431	340	Cohort	112 (1.00)	1023 (1.52)	265 (1.86)	31 (3.10)	M+F	HCC	?	Japan	3.10 (1.41–6.81)
26	Batty et al.	2005	18403	279	Cohort	?	139 (1.00)	122 (1.20)	18 (2.21)	M+F	Colon	?	UK	2.21 (1.29, 3.79)
				190		?	100 (1.00)	81 (1.05)	9 (1.23)		Stomach	?		1.23 (0.59, 2.58)
				147		?	75 (1.00)	69 (1.18)	3 (0.58)		Pancreatic	?		0.58 (0.18, 1.91)
27	Inoue et al.	2008	17590	102	Cohort	?	64 (1.00)	21 (2.07)	17 (2.72)	M+F	HCC	40-69	Japan	2.72 (1.51–4.89)
28	Borena et al.	2011	578200	266	Cohort	36 (1.00)	83 (0.94)	53 (1.02)	94 (1.92)	M+F	liver	?	Norway Austria	1.92 (1.23–2.96)
29	Li et al.	2013	72468	527	Cohort	23 (1.63)	166 (1.36)	65 (1.57)	?	M+F	liver	40-79	Japan	1.57 (1.05–2.60)
30	Campbell et al.	2016	1.57 million	2162	Prospe-ctive	19 (1.41)	586 (1.00)	861 (1.17)	621 (1.75)	M+F	liver	58.2	USA	1.75 (1.56–1.98)
31	Satawan et al.	2015	168476	482	Cohort	?	152 (1.00)	216 (1.24)	114 (1.57)	M+F	HCC	45-77	USA	1.57 (1.31–2.52)
32	Hagstrom et al.	2017	1.2 million	251	Cohort	31 (1.12)	185 (1.14)	25 (1.57)	10 (3.59)	M+F	HCC	?	Sweden	3.59 (1.85 to 6.99)
33	Jeong et al.	2018	510148	7831	Cohort	?	5350 (0.81)	?	2481 (1.19)	M+F	Gastro-intestinal	45-77	Korea	1.19 (1.08, 1.32)
34	Polesel et al.	2008	404	185	Case-control	?	71 (1.00)	76 (1.00)	38 (1.90)	M+F	HCC	40-82	Italy	1.90 (0.9–3.9)
35	Oh et al.	2005	781283	187	Cohort	106 (0.96)	3871 (0.92)	1260 (0.94)	56 (1.25)	M	Stomach	?	Korea	1.25 0.96 to 1.63
36	Rapp et al.	2005	145000	146	Cohort	?	58 (1.00)	75 (1.04)	13 (0.72)	M+F	Stomach	?	Austria	0.72 (0.40–1.33)
				221		?	86 (1.00)	128 (1.56)	7 (2.48)		Colon	?		2.48 (1.15–5.39)
				57		?	18 (1.00)	29 (1.32)	10 (1.67)		Liver	?		1.67 (0.75–3.72)
				64		?	19 (1.00)	31 (1.29)	14 (2.34)		Pancreas	?		2.34 (1.17–4.66)
37	Michaud et al.	2001	163691	350	Cohort	104 (1.00)	73 (1.08)	126 (1.36)	47 (1.74)	M+F	Pancreas	30-75	USA	1.74 (1.17–4.66)
38	Luo et al.	2008	138503	251	Cohort	25 (0.8)	62 (1.00)	84 (0.90)	80 (0.95)	F	Pancreas	50-79	USA	0.95 (0.5 – 1.3)
39	Lin et al.	2007	110792	402	Cohort	79 (1.13)	250 (1.06)	78 (1.09)	5 (0.81)	M+F	Pancreas	?	Japan	0.81 (0.08–4.16)
40	Patel et al.	2004	145627	242	Cohort	?	94 (1.00)	90 (1.03)	58 (2.08)	M+F	Pancreas	?	USA	2.08 (1.48-2.93)
41	Larsson et al.	2005	83140	128	Cohort	5 (0.96)	50 (1.00)	54 (1.25)	19 (1.81)	M+F	Pancreas	?	Sweden	1.81 (1.04 – 3.15)
42	Luo et al.	2007	99670	224	Cohort	51 (1.15)	118 (1.00)	55 (0.95)	?	M+F	Pancreas	?	Japan	0.95 (0.4–1.2)
43	Solomon et al.	2007	495035	654	Cohort	?	194 (1.00)	311 (1.26)	149 (1.33)	M+F	Pancreas	50-71	USA	1.45 (1.04, 2.02)
44	Solomon et al.	2013	501698	2122	Cohort	25 (1.18)	689 (1.00)	934 (1.09)	474 (1.22)	M+F	Pancreas	50-71	USA	1.22 (1.07, 1.55)
45	Nothlings et al.	2007	167430	472	Cohort	?	245 (1.00)	156 (0.89)	75 (1.08)	M+F	Pancreas	?	USA	1.08 (1.02, 2.26)
46	Samanic et al.	2006	362552	320	Cohort	?	184 (1.00)	110 (0.76)	26 (1.14)	M	Oesophagus	34.3	Sweden	1.14 (0.76–1.73)
				1362		?	626 (1.00)	610 (1.08)	126 (1.36)		Rectum	34.3		1.36 (1.13–1.66)
				297		?	115 (1.00)	126 (1.29)	56 (3.62)		Liver	34.3		3.62 (2.62–5.00)
				698		?	352 (1.00)	289 (0.95)	57 (1.16)		Pancreas	34.3		1.16 (0.87–1.53)
				1795		?	763 (1.00)	842 (1.24)	190 (1.74)		Colon	34.3		1.74 (1.48–2.04)
47	Isaksson et al.	2002	21884	176	Cohort	25 (1.02)	31 (1.00)	35 (1.28)	36 (1.46)	M+F	Pancreas	56	Sweden	1.46 (0.87–2.45)
48	Zohar Levi	2018	1794570	551	Cohort	39	420	465	36	M+F	Pancreas	?	Israel	3.79

	et al.					(1.33)	(1.00)	(1.53)	(3.79)					(2.53-5.36)
49	Campbell et al.	2010	2684	1794	Case-control	26 (1.14)	627 (1.00)	660 (1.16)	434 (1.56)	M+F	Colorectal	?	USA	1.56 (1.33 to 2.40)
50	Engeland et al.	2005	2 million	47117	Cohort	388 (0.94)	22568 (1.00)	18733 (1.08)	5428 (1.23)	M+F	Colorectal	?	Norway	1.23 (1.32–1.48)
51	Calle et al.	2003	900000	596	Cohort	?	222 (1.00)	296 (1.13)	102 (3.21)	M+F	Liver	39-79	USA	3.21 (2.94–6.94)
52	Deggard et al.	2011	51251	980	Cohort	76 (1.03)	591 (1.06)	199 (1.05)	114 (1.25)	M+F	Colorectal	45-74	Singapore	1.25 (1.01-1.55)
53	Levi et al.	2011	1.1 million	537	Cohort	89 (1.00)	323 (1.01)	125 (1.43)	?	M	Colorectal	?	Israel	1.43 (1.09–1.89)
54	Hughes et al.	2011	120852	2316	Cohort	?	1372 (0.96)	469 (0.98)	476 (1.11)	M+F	Colorectal	55-69	Nether Land	1.11 0.96- 1.62
55	Basset et al.	2010	39548	569	Cohort	77 (0.77)	97 (1.00)	262 (1.07)	133 (1.25)	M+F	Colorectal	40-69	Australia	1.25 (1.00-2.28)
56	Oxetenko et al.	2010	36941	1464	Cohort	19 (1.62)	495 (1.00)	548 (1.12)	402 (1.39)	F	Colorectal	50-69	USA	1.39 (1.10–2.22)

Most of the studies showed a close association between obesity and different types of gastrointestinal cancer. The pooled RR for overall 56 studies in favour of gastrointestinal cancer (GI) risk was recorded as RR = 1.742, 95% (the black diamond) CI (1.54 - 1.96). This shows that obesity is significantly associated with gastrointestinal cancer risk (figure 2a). For the measurement of heterogeneity, the value of I was I^2 = 92.8% 92% of observed variance between studies is due to real difference in effect size and only 08% of observed variance should be expected to base on random error and tau^2 value was 0.157.No obvious asymmetry was found in the funnel plot as evident from the figure 2b indicating no significant biasness in the studies included in meta-analysis.

(a)



(b)

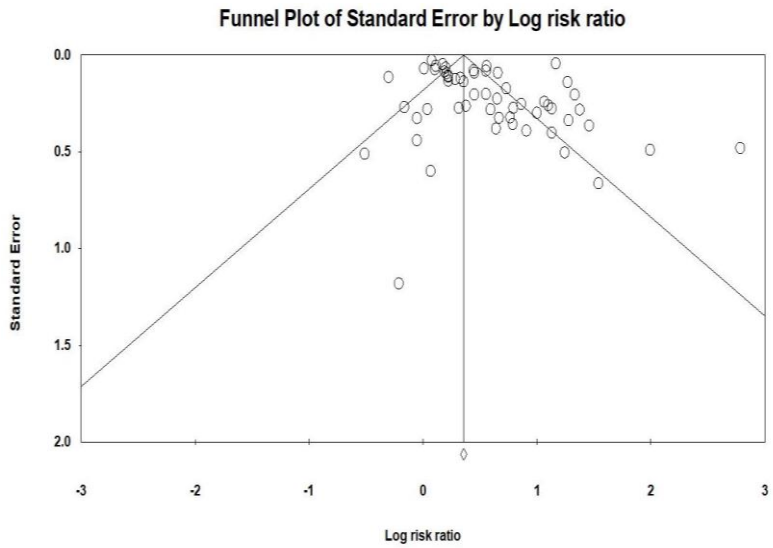


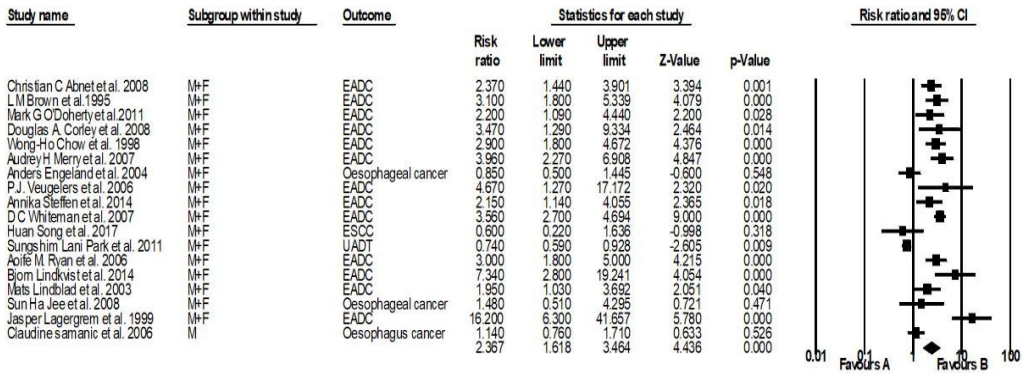
Fig. 2: (a)Forest plot of Risk ratio with a random-effects model for pooled risk ratios of gastrointestinal cancers (Favours A= little or no risk, Favours B= gastrointestinal cancer risk) (b) Funnel plot of risk ratio with a random-effects model for overall biasness in included studies

Following are the results for subgroup analysis performed separately for each gastrointestinal cancer type.

b- Oesophagus Cancer

The pooled RR for oesophageal cancer risk was found to be, RR = 2.376, 95% CI (1.61 – 3.46) showing a significant association between obesity and oesophagus cancer. The I^2 = 89.9% showing heterogeneity among studies and tau^2 = 0.55 as variance measure. Figure 3a,b shows the forest plot and funnel plot for association between obesity and oesophagus cancer and publication bias which is insignificant.

(a)



(b)

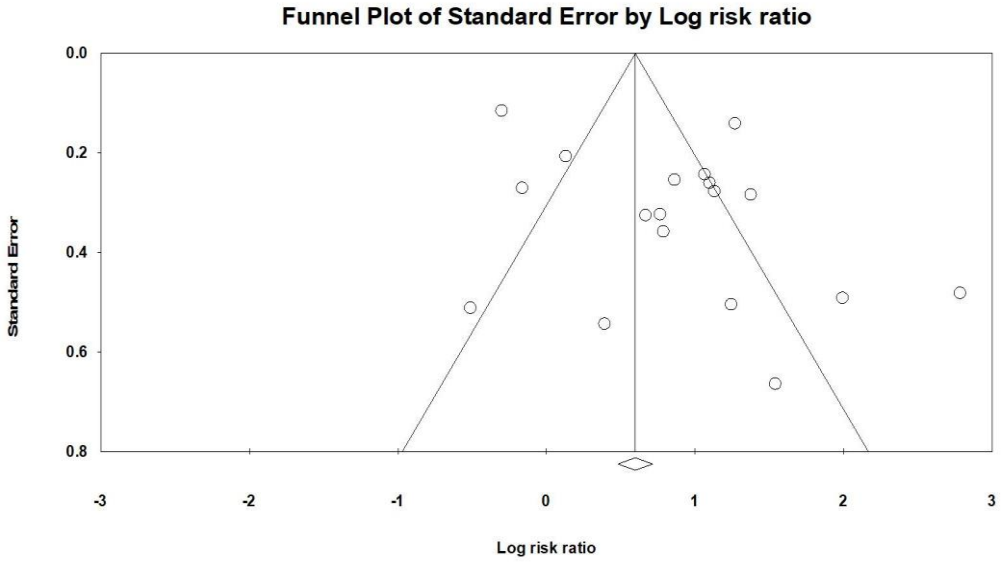
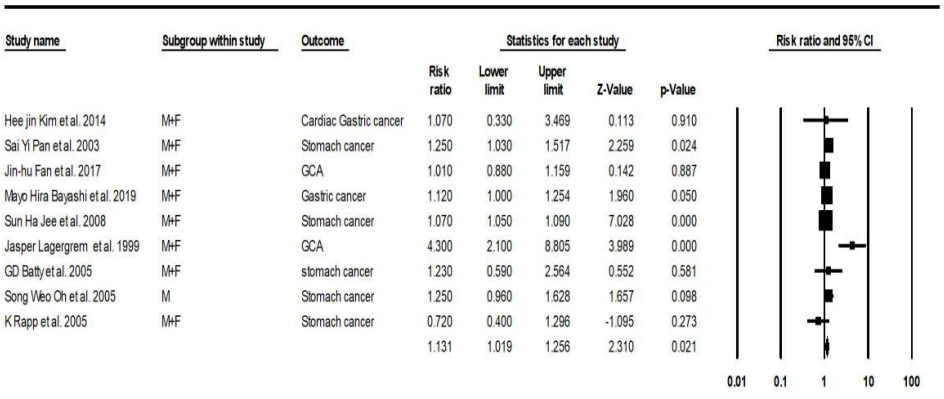


Fig. 3: (a) Forest plot of risk ratio with a random-effects model for risk ratio in oesophagus cancer studies (b) Funnel plot of risk ratio with a random-effects model for overall biasness in oesophagus cancer studies

c- Stomach/ Gastric cancer

The pooled RR for stomach cancer risk was RR = 1.131, 95% CI (1.01 – 1.25) showing a positive association between obesity and stomach cancer. The I^2 = 62.5% showing heterogeneity among studies and tau^2 = 0.01 as variance measure. Figure 4a, b shows the forest plot and funnel plot for association between obesity and stomach cancer and publication bias which is insignificant.

(a)



(b)

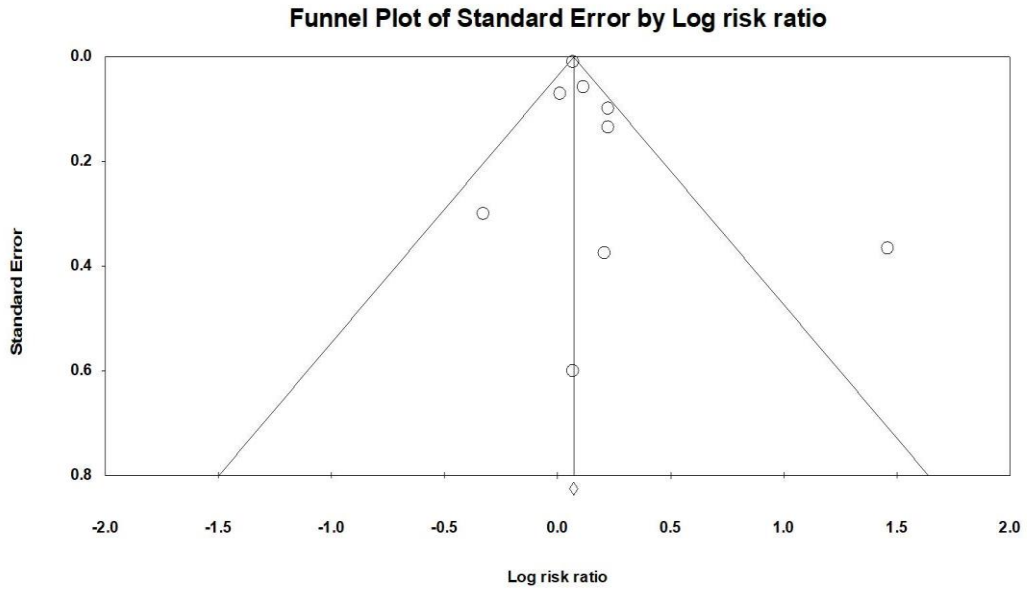
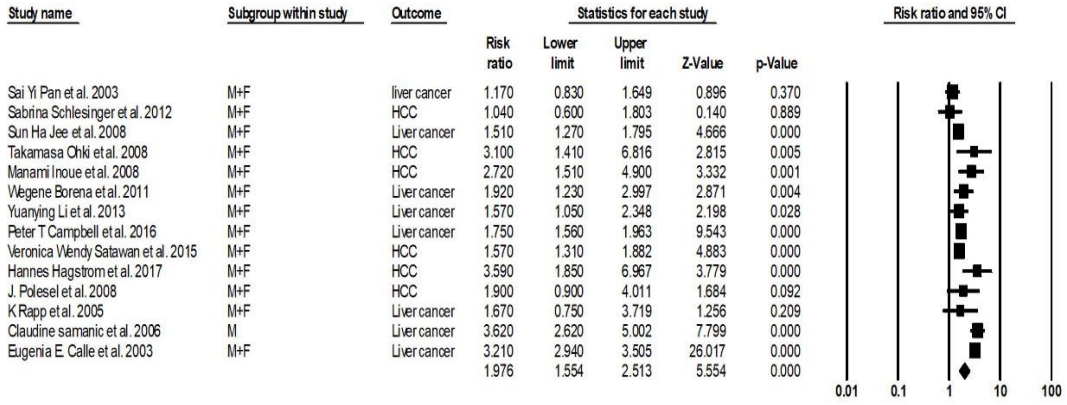


Fig. 4: (a) Forest plot of risk ratio with a random-effects model for risk ratio in stomach cancer studies (b) Funnel plot of risk ratio with a random-effects model for overall biasness in stomach cancer studies

d- Liver Cancer

The pooled RR for liver cancer risk was RR = 1.976, 95% CI (1.55 – 2.51) showing a significant association between obesity and liver cancer. The I^2 = 91.5% showing heterogeneity among studies and tau^2 = 0.15 as variance measure. Figure 5a, b shows the forest plot and funnel plot for association between obesity and liver cancer and publication bias which is insignificant.

(a)



(b)

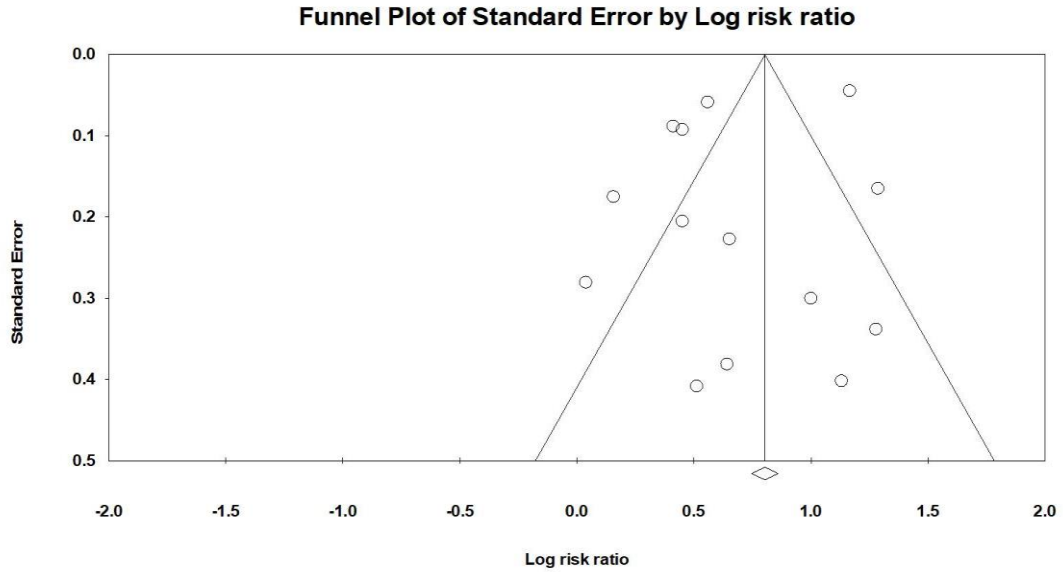
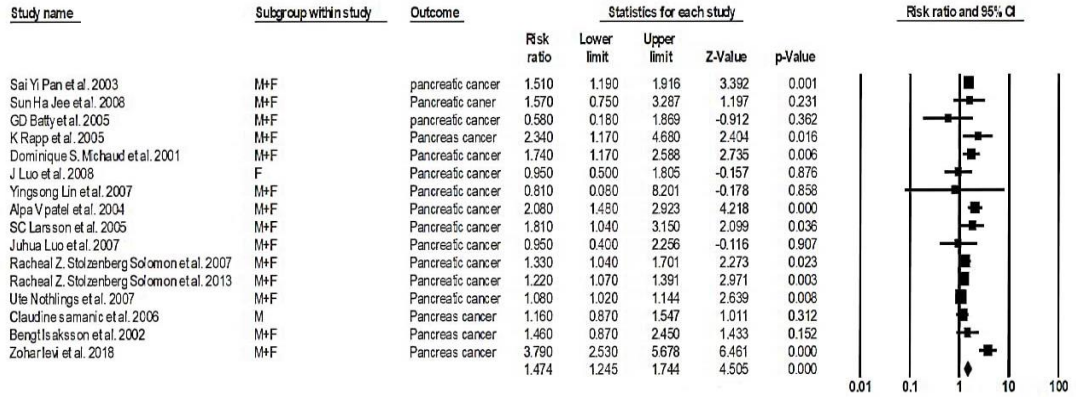


Fig. 5: (a) Forest plot of risk ratio with a random-effects model for risk ratio in liver cancer studies (b) Funnel plot of risk ratio with a random-effects model for overall biasness in liver cancer studies

e- Pancreatic Cancer

The pooled RR for pancreatic cancer risk was RR = 1.474, 95% CI (1.24 – 1.74) showing a significant association between obesity and pancreatic cancer. The I^2 = 78% showing heterogeneity among studies and tau^2 = 0.06 as variance measure. Figure 6a, b shows the forest plot and funnel plot for association between obesity and pancreatic cancer and publication bias which is insignificant.

(a)



Study name	Subgroup within study	Outcome	Statistics for each study: Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Sai Yi Pan et al. 2003	M+F	pancreatic cancer	1.510	1.190	1.916	3.392	0.001
Sun Ha Jee et al. 2008	M+F	Pancreatic caner	1.570	0.750	3.287	1.197	0.231
GD Batty et al. 2005	M+F	pancreatic cancer	0.580	0.180	1.869	-0.912	0.362
K Rapp et al. 2005	M+F	Pancreas cancer	2.340	1.170	4.680	2.404	0.016
Dominique S. Michaud et al. 2001	M+F	Pancreatic cancer	1.740	1.170	2.588	2.735	0.006
J Luo et al. 2008	F	Pancreatic cancer	0.950	0.500	1.805	-0.157	0.876
Yingsong Lin et al. 2007	M+F	Pancreatic cancer	0.810	0.080	8.201	-0.178	0.858
Alpa V patel et al. 2004	M+F	Pancreatic cancer	2.080	1.480	2.923	4.218	0.000
SC Larsson et al. 2005	M+F	Pancreatic cancer	1.810	1.040	3.150	2.099	0.036
Juhua Luo et al. 2007	M+F	Pancreatic cancer	0.950	0.400	2.256	-0.116	0.907
Racheal Z. Stolzenberg Solomon et al. 2007	M+F	Pancreatic cancer	1.330	1.040	1.701	2.273	0.023
Racheal Z. Stolzenberg Solomon et al. 2013	M+F	Pancreatic cancer	1.220	1.070	1.391	2.971	0.003
Ute Nothlings et al. 2007	M+F	Pancreatic cancer	1.080	1.020	1.144	2.639	0.008
Claudine samanic et al. 2006	M	Pancreas cancer	1.160	0.870	1.547	1.011	0.312
Bengt Isaksson et al. 2002	M+F	Pancreas cancer	1.460	0.870	2.450	1.433	0.152
Zohar levi et al. 2018	M+F	Pancreas cancer	3.790	2.530	5.678	6.461	0.000
			1.474	1.245	1.744	4.505	0.000

(b)

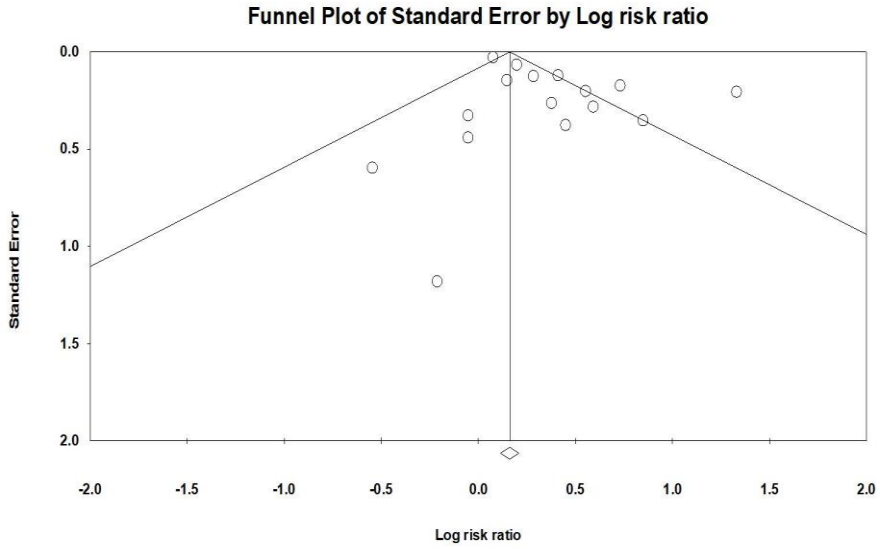


Fig. 6: (a) Forest plot of risk ratio with a random-effects model for risk ratio in pancreatic cancer studies (b) Funnel plot of risk ratio with a random-effects model for overall biasness in pancreatic cancer studies

f- Colorectal Cancer

The pooled RR for colorectal cancer risk was RR = 1.428, 95% CI (1.27 – 1.60) showing a significant association between obesity and colorectal cancer. The I^2 = 71% showing heterogeneity among studies and tau^2 = 0.029 as variance measure. Figure 7 shows the forest plot and funnel plot for association between obesity and colorectal cancer and publication bias which is insignificant.

(a)

Study name	Subgroup within study	Outcome	Statistics for each study					Risk ratio and 95% CI
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	
Xuesong Han et al. 2014	M+F	colorectal cancer	1.370	0.800	2.346	1.147	0.251	
Sai Yi Pan et al. 2003	M+F	colon cancer	1.930	1.610	2.314	7.109	0.000	
Sun Ha Jee et al. 2008	M+F	Colon cancer	1.210	1.020	1.435	2.187	0.029	
GD Batty et al. 2005	M+F	colon cancer	2.210	1.290	3.786	2.887	0.004	
K Rapp et al. 2005	M+F	Colon cancer	2.480	1.150	5.348	2.316	0.021	
Claudine samanic et al. 2006	M	Colon cancer	1.740	1.480	2.046	6.708	0.000	
Peter T. Campbell et al. 2010	M+F	Colorectal cancer	1.560	1.330	1.830	5.464	0.000	
Ander Engeland et al. 2005	M+F	Colorectal cancer	1.230	1.020	1.483	2.167	0.030	
Andrew O. deggard et al. 2011	M+F	Colorectal cancer	1.250	1.010	1.547	2.051	0.040	
Zohar levi et al. 2011	M	Colorectal cancer	1.430	1.090	1.876	2.582	0.010	
Laura AE. Hughes et al. 2011	M+F	Colorectal cancer	1.110	0.960	1.283	1.409	0.159	
Julie K. Basset et al. 2010	M+F	Colorectal cancer	1.250	1.000	1.563	1.960	0.050	
Amy S. Oxetenko et al. 2010	F	Colorectal cancer	1.390	1.100	1.756	2.758	0.006	
			1.428	1.271	1.606	5.969	0.000	

(b)

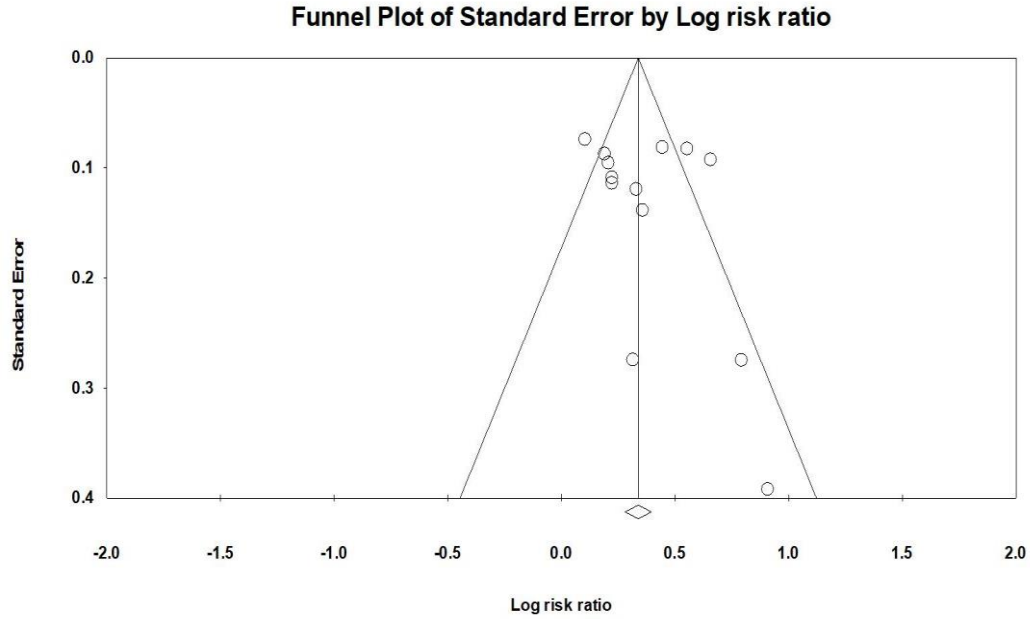


Fig. 7: (a) Forest plot of risk ratio with a random-effects model for risk ratio in colorectal cancer studies (b) Funnel plot of risk ratio with a random-effects model for overall biasness in colorectal cancer studies

DISCUSSION

Gastrointestinal cancer is one of the leading causes of mortality worldwide. According to statistics, gastrointestinal cancer is the reason of death of 1/3 cancer patients (Arnold et al., 2020).Obesity plays an important role in the development of gastrointestinal but a clear relation between two is missing. We performed this meta-analysis with 56 eligible studies after considerable scrutiny to find the association between obesity and risk of gastrointestinal cancer incidence. In almost all studies, BMI was used as a measure of obesity. Most of the studies showed up strong positive association between obesity and different types of gastrointestinal cancer risk and mortality.

The meta-analysis results described that obesity significantly increases the risk of overall gastrointestinal cancer (RR = 1.742). According to results the type of gastrointestinal cancer which was strongly related with obesity was oesophageal cancer compared to all other gastrointestinal cancers (RR = 2.376). Random effect model was applied to determine effect size and heterogeneity. Random effect model considered variations among all studies included in the meta-analysis. Every

study reported a different effect size (RR) due to changes in subject's characteristics of each study.

Weight loss activities for obese people can decrease the overall risk of gastrointestinal cancer. This association between obesity and overall risk of gastrointestinal tract cancers may be due to some mechanisms which are related with adipose tissue production of adipokinesis and vascular growth factors, changes in immune system functions and endocrine disruptors (De Pergola Silvestris, 2013).

Excess adiposity is recognized as the second major cause of cancer, after smoking. There are different hypotheses at present which provide a convincing link between obesity and gastrointestinal cancer. First one is altered insulin signaling. According to this, Excess adiposity leads to insulin resistance causing hyper-insulinemia. High concentration of insulin in blood which is a mitogenic hormone activates MAP-Kinase resulting in cell proliferation causing cancer. Second is chronic inflammation which is the result of excessive accumulation of visceral fat causing improper activation of pro-inflammatory signals and cytokine production. This condition results in the release of free fatty acids in circulation and macrophages. Free fatty acids cause the activation of NF-kB factors which may results in the development of gastric cancer. Adipose tissues stimulate the production of sex hormones particularly estrone and estradiol. It causes the stimulation of IGF-1 receptor and help in cell proliferation causing cancer (Karczewski et al., 2019).

But more deep study is required to fully understand the underlying mechanism (De Pergola Silvestris, 2013). Also, people with BMI less than 25 kg/m^2 were seen to be at lower risk of developing gastrointestinal cancer.

CONCLUSION

It was concluded by this study that obese people were at greater risk of developing different types of gastrointestinal cancer as compared to non-obese even at early age.

ETHICAL APPROVAL

The ethical approval was not implemented.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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