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% CI. 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 24.9 kg/m² range represents the normal BMI, whereas BMI greater than 25 kg/m ² represents overweight persons and a BMI greater than 30 kg/m² represent obese. If BMI exceeds 40 kg/m², 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% CIs. 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/m² in one category, another risk estimate for 35 to 40 kg/m² 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 I² 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>Year</th>
<th>Control</th>
<th>Patients</th>
<th>Type of study</th>
<th>No. of patients with BMI</th>
<th>Gender</th>
<th>Type of GIT cancer</th>
<th>Geo Location</th>
<th>Age</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abnet et al.</td>
<td>2008</td>
<td>480,475</td>
<td>371</td>
<td>Cohort</td>
<td>2 (1,61)</td>
<td>M+F</td>
<td>EADC</td>
<td>USA</td>
<td>50-71</td>
<td>2.37 (1.44–3.59)</td>
</tr>
<tr>
<td>2</td>
<td>Brown et al.</td>
<td>1995</td>
<td>750</td>
<td>174</td>
<td>Case control</td>
<td>31 (1.1)</td>
<td>M</td>
<td>EADC</td>
<td>USA</td>
<td>30-79</td>
<td>5.1 (1.8-5.3)</td>
</tr>
<tr>
<td>3</td>
<td>O’Doherty et al.</td>
<td>2011</td>
<td>218854</td>
<td>253</td>
<td>Cohort</td>
<td>79 (3.1)</td>
<td>M+F</td>
<td>EADC</td>
<td>USA</td>
<td>50-71</td>
<td>2.20 (1.09 to 4.09)</td>
</tr>
<tr>
<td>4</td>
<td>Carley et al.</td>
<td>2008</td>
<td>206974</td>
<td>101</td>
<td>Nested Case-control</td>
<td>104 (2.09)</td>
<td>M+F</td>
<td>EADC</td>
<td>USA</td>
<td>?</td>
<td>3.47 (1.29-9.33)</td>
</tr>
<tr>
<td>5</td>
<td>Chow et al.</td>
<td>1998</td>
<td>695</td>
<td>554</td>
<td>Case-control</td>
<td>99 (2.90)</td>
<td>M+F</td>
<td>EADC</td>
<td>USA</td>
<td>30-79</td>
<td>2.90 (1.8-4.7)</td>
</tr>
<tr>
<td>6</td>
<td>Merry et al.</td>
<td>2007</td>
<td>120852</td>
<td>133</td>
<td>Cohort</td>
<td>19 (3.96)</td>
<td>M+F</td>
<td>EADC</td>
<td>Nether land</td>
<td>55-69</td>
<td>3.96 (2.27 to 6.88)</td>
</tr>
<tr>
<td>7</td>
<td>Engelhard et al.</td>
<td>2004</td>
<td>2 million</td>
<td>2245</td>
<td>Cohort</td>
<td>42 (7.34)</td>
<td>M+F</td>
<td>EADC</td>
<td>Norway</td>
<td>20-74</td>
<td>0.85 (0.50-0.82)</td>
</tr>
<tr>
<td>8</td>
<td>Veuergers et al.</td>
<td>2006</td>
<td>102</td>
<td>57</td>
<td>Case-control</td>
<td>4 (0.60)</td>
<td>M+F</td>
<td>EADC</td>
<td>Canada</td>
<td>?</td>
<td>4.67 (1.27-17.19)</td>
</tr>
<tr>
<td>9</td>
<td>Seifert et al.</td>
<td>2014</td>
<td>395456</td>
<td>124</td>
<td>Cohort</td>
<td>33 (2.15)</td>
<td>M+F</td>
<td>EADC</td>
<td>UK</td>
<td>20-70</td>
<td>2.14 (1.4-4.05)</td>
</tr>
<tr>
<td>10</td>
<td>Whiteman et al.</td>
<td>2007</td>
<td>1580</td>
<td>801</td>
<td>Case-control</td>
<td>130 (3.56)</td>
<td>M+F</td>
<td>EADC</td>
<td>Australia</td>
<td>18-79</td>
<td>3.56 (2.7 to 3.36)</td>
</tr>
<tr>
<td>11</td>
<td>Song et al.</td>
<td>2017</td>
<td>96331</td>
<td>342</td>
<td>cohort</td>
<td>4 (0.60)</td>
<td>M+F</td>
<td>ESCC</td>
<td>Japan</td>
<td>40-69</td>
<td>0.60 (0.22-1.61)</td>
</tr>
<tr>
<td>12</td>
<td>Han et al.</td>
<td>2014</td>
<td>13901</td>
<td>298</td>
<td>Cohort</td>
<td>17 (1.37)</td>
<td>M</td>
<td>Colorectal</td>
<td>USA</td>
<td>45-64</td>
<td>0.37 (0.83-3.11)</td>
</tr>
<tr>
<td>13</td>
<td>Park et al.</td>
<td>2011</td>
<td>2173</td>
<td>2048</td>
<td>Case-control</td>
<td>252 (0.74)</td>
<td>M+F</td>
<td>UADT</td>
<td>Europe</td>
<td>?</td>
<td>0.74 (0.59 - 0.93)</td>
</tr>
<tr>
<td>14</td>
<td>Ryan et al.</td>
<td>2006</td>
<td>893</td>
<td>283</td>
<td>Case-control</td>
<td>131 (3.00)</td>
<td>M+F</td>
<td>EADC</td>
<td>Ireland</td>
<td>?</td>
<td>3.0 (1.8-5.0)</td>
</tr>
<tr>
<td>15</td>
<td>Lindkvist et al.</td>
<td>2014</td>
<td>578700</td>
<td>114</td>
<td>Cohort</td>
<td>42 (7.34)</td>
<td>M+F</td>
<td>EADC</td>
<td>Australia</td>
<td>?</td>
<td>7.34 (2.8-18.68)</td>
</tr>
<tr>
<td>16</td>
<td>Kim et al.</td>
<td>2014</td>
<td>1288</td>
<td>998</td>
<td>Case-control</td>
<td>26 (1.07)</td>
<td>M+F</td>
<td>Cardiac</td>
<td>South Korea</td>
<td>30-80</td>
<td>1.07 (0.331-2.255)</td>
</tr>
<tr>
<td>17</td>
<td>Pan et al.</td>
<td>2003</td>
<td>5039</td>
<td>1176</td>
<td>Case-control</td>
<td>1176 (1.25)</td>
<td>M+F</td>
<td>Stomach</td>
<td>Canada</td>
<td>20-76</td>
<td>1.25 (1.03, 1.51)</td>
</tr>
<tr>
<td>18</td>
<td>Schliesinger et al.</td>
<td>2012</td>
<td>359525</td>
<td>177</td>
<td>Cohort</td>
<td>95 (1.04)</td>
<td>M+F</td>
<td>BCC</td>
<td>Europe</td>
<td>?</td>
<td>1.04 (0.60-1.83)</td>
</tr>
<tr>
<td>19</td>
<td>Fan et al.</td>
<td>2017</td>
<td>29446</td>
<td>1716</td>
<td>Cohort</td>
<td>390 (1.01)</td>
<td>M+F</td>
<td>GCA</td>
<td>China</td>
<td>?</td>
<td>1.01 (0.88-1.16)</td>
</tr>
<tr>
<td>20</td>
<td>Rayashi et al.</td>
<td>2019</td>
<td>92056</td>
<td>2860</td>
<td>Cohort</td>
<td>301 (1.12)</td>
<td>M+F</td>
<td>Gastric cancer</td>
<td>Japan</td>
<td>40-69</td>
<td>1.12 (1.00 - 1.51)</td>
</tr>
<tr>
<td>21</td>
<td>Lee et al.</td>
<td>2008</td>
<td>1213829</td>
<td>13810</td>
<td>Cohort</td>
<td>242 (1.07)</td>
<td>M+F</td>
<td>Stomach</td>
<td>Korea</td>
<td>30-95</td>
<td>1.07 (1.05-1.64)</td>
</tr>
</tbody>
</table>

Legend:
- GIT: Gastrointestinal Tumor
- RR: Relative Risk
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Cohort</th>
<th>Cases</th>
<th>Control</th>
<th>Case-control Ratio</th>
<th>Case-control Odds Ratio</th>
<th>Control Odds Ratio</th>
<th>p-value</th>
<th>Effect Size</th>
<th>SE</th>
<th>95% CI</th>
<th>p-value</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Lagergren et al.</td>
<td>820</td>
<td>189</td>
<td>10</td>
<td>68 (3.20)</td>
<td>22 (16.20)</td>
<td>34 (4.30)</td>
<td></td>
<td>M+F EADIC</td>
<td></td>
<td>&lt;80</td>
<td>1.11-2.44</td>
<td>Sweden</td>
</tr>
<tr>
<td>1999</td>
<td>Lagergren et al.</td>
<td>820</td>
<td>262</td>
<td>47</td>
<td>100 (1.30)</td>
<td>91 (2.20)</td>
<td>34 (4.30)</td>
<td></td>
<td>M+F GCA</td>
<td></td>
<td>&lt;80</td>
<td>1.21-4.11</td>
<td>Sweden</td>
</tr>
<tr>
<td>2008</td>
<td>Ohtani et al.</td>
<td>1431</td>
<td>340</td>
<td>112</td>
<td>1023 (1.52)</td>
<td>265 (1.86)</td>
<td>31 (3.10)</td>
<td></td>
<td>M+F HCC</td>
<td></td>
<td>?</td>
<td>2.31-7.61</td>
<td>Japan</td>
</tr>
<tr>
<td>2005</td>
<td>Batty et al.</td>
<td>18403</td>
<td>279</td>
<td></td>
<td>139 (1.20)</td>
<td>122 (1.00)</td>
<td>18 (2.21)</td>
<td></td>
<td>M+F Colon</td>
<td></td>
<td>?</td>
<td>2.83-8.18</td>
<td>UK</td>
</tr>
<tr>
<td>2007</td>
<td>Inoue et al.</td>
<td>17590</td>
<td>102</td>
<td>64</td>
<td>21 (2.07)</td>
<td>17 (2.72)</td>
<td></td>
<td></td>
<td>M+F HCC</td>
<td></td>
<td>40-69</td>
<td>0.94-4.89</td>
<td>Japan</td>
</tr>
<tr>
<td>2011</td>
<td>Borzena et al.</td>
<td>578200</td>
<td>266</td>
<td>36</td>
<td>83 (0.94)</td>
<td>53 (1.02)</td>
<td>94 (1.92)</td>
<td></td>
<td>M+F live</td>
<td></td>
<td></td>
<td>1.02-2.96</td>
<td>Norway, Austria</td>
</tr>
<tr>
<td>2013</td>
<td>Li et al.</td>
<td>72468</td>
<td>527</td>
<td>23</td>
<td>166 (1.36)</td>
<td>65 (1.57)</td>
<td></td>
<td></td>
<td>M+F live</td>
<td></td>
<td>40-79</td>
<td>1.57-2.60</td>
<td>Japan</td>
</tr>
<tr>
<td>2016</td>
<td>Campbell et al.</td>
<td>168424</td>
<td>382</td>
<td></td>
<td>152 (2.21)</td>
<td>114 (1.57)</td>
<td></td>
<td></td>
<td>M+F HCC</td>
<td></td>
<td>45-77</td>
<td>1.31-2.52</td>
<td>Sweden</td>
</tr>
<tr>
<td>2017</td>
<td>Haggstrom et al.</td>
<td>720283</td>
<td>187</td>
<td>106</td>
<td>387 (0.92)</td>
<td>1200 (0.94)</td>
<td>56 (1.25)</td>
<td></td>
<td>M+F Stomach</td>
<td></td>
<td></td>
<td>1.25-1.63</td>
<td>Korea</td>
</tr>
<tr>
<td>2005</td>
<td>Rapp et al.</td>
<td>145000</td>
<td>146</td>
<td>58</td>
<td>75 (1.04)</td>
<td>13 (0.72)</td>
<td></td>
<td></td>
<td>M+F Stomach</td>
<td></td>
<td></td>
<td>0.72-1.37</td>
<td>Austria</td>
</tr>
<tr>
<td>2007</td>
<td>Lin et al.</td>
<td>110792</td>
<td>402</td>
<td>86</td>
<td>128 (1.56)</td>
<td>10 (2.48)</td>
<td></td>
<td></td>
<td>M+F Colon</td>
<td></td>
<td></td>
<td>2.48-5.39</td>
<td>Japan</td>
</tr>
<tr>
<td>2005</td>
<td>Patel et al.</td>
<td>83140</td>
<td>128</td>
<td>50</td>
<td>51 (1.25)</td>
<td>19 (1.81)</td>
<td></td>
<td></td>
<td>M+F Pancreas</td>
<td></td>
<td></td>
<td>1.81-3.51</td>
<td>Sweden</td>
</tr>
<tr>
<td>2017</td>
<td>Luo et al.</td>
<td>99670</td>
<td>224</td>
<td>51</td>
<td>118 (1.00)</td>
<td>55 (0.95)</td>
<td></td>
<td></td>
<td>M+F Pancreas</td>
<td></td>
<td></td>
<td>0.95-1.42</td>
<td>Japan</td>
</tr>
<tr>
<td>2007</td>
<td>Solomon et al.</td>
<td>495035</td>
<td>654</td>
<td>194</td>
<td>311 (1.26)</td>
<td>149 (1.33)</td>
<td></td>
<td></td>
<td>M+F Pancreas</td>
<td></td>
<td></td>
<td>1.45-2.02</td>
<td>USA</td>
</tr>
<tr>
<td>2013</td>
<td>Solomon et al.</td>
<td>501698</td>
<td>2122</td>
<td>25</td>
<td>689 (1.00)</td>
<td>934 (1.09)</td>
<td>474 (2.24)</td>
<td></td>
<td>M+F Pancreas</td>
<td></td>
<td></td>
<td>1.22-1.55</td>
<td>USA</td>
</tr>
<tr>
<td>2007</td>
<td>Nothlings et al.</td>
<td>167430</td>
<td>472</td>
<td>245</td>
<td>156 (0.89)</td>
<td>75 (1.08)</td>
<td></td>
<td></td>
<td>M+F Pancreas</td>
<td></td>
<td></td>
<td>0.98-2.26</td>
<td>USA</td>
</tr>
<tr>
<td>2006</td>
<td>Samaniego et al.</td>
<td>362552</td>
<td>320</td>
<td>184</td>
<td>110 (0.76)</td>
<td>26 (1.14)</td>
<td></td>
<td></td>
<td>M+Oesophagus</td>
<td></td>
<td>34.3</td>
<td>1.14-1.37</td>
<td>Sweden</td>
</tr>
<tr>
<td>2007</td>
<td>Rapp et al.</td>
<td>145000</td>
<td>146</td>
<td>50</td>
<td>54 (1.56)</td>
<td>128 (1.56)</td>
<td></td>
<td></td>
<td>M+Rectum</td>
<td></td>
<td>34.3</td>
<td>1.14-1.37</td>
<td>USA</td>
</tr>
<tr>
<td>2007</td>
<td>Solomon et al.</td>
<td>501698</td>
<td>2122</td>
<td>25</td>
<td>689 (1.00)</td>
<td>934 (1.09)</td>
<td>474 (2.24)</td>
<td></td>
<td>M+Liver</td>
<td></td>
<td>34.3</td>
<td>1.14-1.37</td>
<td>Austria</td>
</tr>
<tr>
<td>2007</td>
<td>Solomon et al.</td>
<td>501698</td>
<td>2122</td>
<td>25</td>
<td>689 (1.00)</td>
<td>934 (1.09)</td>
<td>474 (2.24)</td>
<td></td>
<td>M+Colon</td>
<td></td>
<td>34.3</td>
<td>1.14-1.37</td>
<td>USA</td>
</tr>
<tr>
<td>2007</td>
<td>Zohar Levi</td>
<td>1794570</td>
<td>551</td>
<td>39</td>
<td>420 (1.00)</td>
<td>465 (1.46)</td>
<td>36 (1.46)</td>
<td></td>
<td>M+F Pancreas</td>
<td></td>
<td></td>
<td>0.98-2.26</td>
<td>Israel</td>
</tr>
</tbody>
</table>
Association of Obesity and Gastrointestinal Cancer - A Meta-Analysis

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 I² was I² = 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 tau² 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.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Year</th>
<th>Cohort</th>
<th>Gender</th>
<th>Cancer Type</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al.</td>
<td>2010</td>
<td>2684</td>
<td>M+F</td>
<td>Colorectal</td>
<td>1.33</td>
<td>(1.14 - 1.53)</td>
</tr>
<tr>
<td>Engeland et al.</td>
<td>2005</td>
<td>2 million</td>
<td>M+F</td>
<td>Colorectal</td>
<td>1.36</td>
<td>(1.13 to 2.40)</td>
</tr>
<tr>
<td>Calle et al.</td>
<td>2003</td>
<td>900000</td>
<td>M+F</td>
<td>Liver</td>
<td>3.79</td>
<td>(2.53 - 5.36)</td>
</tr>
<tr>
<td>Deggard et al.</td>
<td>2011</td>
<td>51251</td>
<td>M+F</td>
<td>Colorectal</td>
<td>1.74</td>
<td>(1.54 - 1.96)</td>
</tr>
<tr>
<td>Levi et al.</td>
<td>2011</td>
<td>1.1 million</td>
<td>M</td>
<td>Colorectal</td>
<td>1.43</td>
<td>(1.09 - 1.89)</td>
</tr>
<tr>
<td>Hughes et al.</td>
<td>2011</td>
<td>120852</td>
<td>M+F</td>
<td>Colorectal</td>
<td>5.56</td>
<td>(4.09 - 7.33)</td>
</tr>
<tr>
<td>Basset et al.</td>
<td>2010</td>
<td>39548</td>
<td>M+F</td>
<td>Colorectal</td>
<td>1.25</td>
<td>(1.01 - 1.55)</td>
</tr>
<tr>
<td>Oxetenko et al.</td>
<td>2010</td>
<td>36941</td>
<td>F</td>
<td>Colorectal</td>
<td>1.39</td>
<td>(1.10 - 2.22)</td>
</tr>
</tbody>
</table>

LGU. J. Life Sci 7(1): LGUJLS MS.ID- 165 (2023)
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.
**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.
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 I² = 91.5% showing heterogeneity among studies and τ² = 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.
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.
Association of Obesity and Gastrointestinal Cancer - A Meta-Analysis

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.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Outcome</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuesong Han et al. 2014</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.370</td>
<td>0.800</td>
<td>2.346</td>
<td>1.147</td>
<td>0.251</td>
</tr>
<tr>
<td>Sai Y. Pan et al. 2003</td>
<td>M</td>
<td>colon cancer</td>
<td>1.930</td>
<td>1.610</td>
<td>2.314</td>
<td>7.109</td>
<td>0.000</td>
</tr>
<tr>
<td>Sung Ho Lee et al. 2008</td>
<td>M</td>
<td>colon cancer</td>
<td>2.110</td>
<td>1.920</td>
<td>1.465</td>
<td>1.217</td>
<td>0.026</td>
</tr>
<tr>
<td>GD Bohl et al. 2005</td>
<td>M</td>
<td>colon cancer</td>
<td>2.310</td>
<td>1.920</td>
<td>3.786</td>
<td>6.887</td>
<td>0.004</td>
</tr>
<tr>
<td>K Rapp et al. 2006</td>
<td>M</td>
<td>colon cancer</td>
<td>2.480</td>
<td>1.950</td>
<td>3.548</td>
<td>2.316</td>
<td>0.021</td>
</tr>
<tr>
<td>Claudine samarinic et al. 2006</td>
<td>M</td>
<td>colon cancer</td>
<td>1.740</td>
<td>1.480</td>
<td>2.064</td>
<td>6.708</td>
<td>0.000</td>
</tr>
<tr>
<td>Peter T. Campbell et al. 2010</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.950</td>
<td>1.330</td>
<td>2.304</td>
<td>5.844</td>
<td>0.000</td>
</tr>
<tr>
<td>Andre Ebi@dard et al. 2003</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.330</td>
<td>1.020</td>
<td>1.643</td>
<td>1.217</td>
<td>0.026</td>
</tr>
<tr>
<td>Andrew O. deggardard et al. 2011</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.250</td>
<td>1.010</td>
<td>1.547</td>
<td>2.051</td>
<td>0.040</td>
</tr>
<tr>
<td>Zohar levi et al. 2011</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.430</td>
<td>1.090</td>
<td>1.876</td>
<td>2.582</td>
<td>0.010</td>
</tr>
<tr>
<td>Laura AE. Hughes et al. 2011</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.110</td>
<td>0.860</td>
<td>1.283</td>
<td>1.409</td>
<td>0.158</td>
</tr>
<tr>
<td>Julie K. Brown et al. 2010</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.250</td>
<td>1.000</td>
<td>1.593</td>
<td>1.980</td>
<td>0.050</td>
</tr>
<tr>
<td>Amy S. Brown et al. 2010</td>
<td>M</td>
<td>colorectal cancer</td>
<td>1.428</td>
<td>1.271</td>
<td>1.606</td>
<td>9.699</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Association of Obesity and Gastrointestinal Cancer- A Meta-Analysis

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/m² 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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46. Larsson SC, Permert J, Håkansson N, Näslund I, Bergkvist L, Wolk A (2005). Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of


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