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The Association between Obesity and Cancer

Melissa Kazan* and İskender Karalti

Department of Nutrition & Dietetics, Yeditepe University, Istanbul-34000, Turkey

Abstract

The prevalence of overweight and obesity has ascended from 15% in 1980 to 35% in 2005 and it will continue to increase in the future. Almost 22% of the whole cancer cases resulted from obesity and overweight according to the research done by Wolin et al. From multiple adequate evidences, it has been recorded about that obesity importantly causes a lot of types of cancer such as adenocarcinoma of esophagus, colorectal cancer, endometrial cancer (the lining of the uterus), post-menopausal breast cancer and renal cell cancer. Furthermore, obesity can lead to elevate other cancer risk the kind of gallbladder cancer, pancreatic cancer, hepatocellular cancer (subtype of liver cancer), thyroid cancer, cervical cancer (adenocarcinoma of the cervix), Non-Hodgkin Lymphoma (NHL), leukemia, multiple myeloma and malignant melanoma (a type of skin cancer). The attributable risks are 46% for endometrial cancer, 41% for gallbladder cancer between females, 40% for adenocarcinoma of esophagus between males, 37% for adenocarcinoma of esophagus between females, 27% for kidney cancer between females, 22% for kidney cancer between males, 22% for colon cancer between males, and 16% for breast cancer respectively in the 2008 meta-analysis. In addition, current investigations asserted that the attributable risks for all cancers are approximately 5% between males and 6% between females by associating with obesity and overweight in the UK. However, the mechanisms between cancer risk and obesity are uncertain and can be different according to the cancer types and also associated with the fat distribution in organism. Therefore, between some cancer types, waist hip ratio and waist circumference have been found to be more relevant than BMI because abdominal obesity can be diagnosed better with waist hip ratio and waist circumference. Generally, increased plasma insulin levels, elevated IGF-1 synthesis, reduced IGFBP-1 synthesis, and low plasma SHBG levels can be shown for mechanism of many of cancer types. In addition, adipokines can also be added in these mechanisms.

Keywords: Obesity; Cancer; Body mass index; Mechanisms

Abbreviations: BMI: Body Mass Index; RR: Relative Risk; OR: Odds Ratio; NHL: Non-Hodgkin Lymphoma; ESCC or SCC: Oesophageal Squamous Cell Carcinomas; EAC or AC: Oesophageal Adenocarcinomas; GERD or GORD: Gastro Oesophageal Reflux Disease; BE: Barrett's Oesophagus; GLOBOCAN: Global Cancer Statistics; IGF: Insulin Like Growth Factor; IGFBP: Insulin Like Growth Factor Binding Proteins; SHBG: Sex Hormone Binding Globulin; HRT: Hormone Replacement Therapy; WHO: World Health Organization; WHR: Waist To Hip Ratio; EPIC: European Prospective Investigation Into Cancer And Nutrition

Introduction

The definition of obesity is based on Body Mass Index (BMI], which is body weight (kg): height (m²) [1]. While BMI of ≥30.0 kg/m² is defined as obesity, BMI between 25.0 and 29.9 kg/m² is specified as overweight [2] (Table 1). The prevalence of obesity and overweight in children, adolescents, and adults has increased considerably over previous decades mostly in industrialized countries, and in the future a further growing is predicted. According to estimates by the World Health Organization (WHO), 1.6 billion adults over the age of 15 and 20 million children (age <5) were overweight, as obese adults were 400 million in 2005. In addition to this, in April 2007, the International Association provided the information for the Study of Obesity overweight adults in the EU were approximately 40-50% of men and 25-35% women, and an appendage 15-25% of men and 15-25% of women were obese. In like manner, overweight people in the US were approximately 34.1% of the population and almost 32.2% of the population were obese in 2004 [2-4]. In 2007-2008, the prevalence of obesity was 33.8% of the US adults and about 68.0% were overweight, after regulating for age. This is why obesity is one of the most important health issues in the developed world and also in many developing countries [3-5].

According to the researches, obesity causes severe health problems such as cardiovascular diseases, type II diabetes, dyslipidemia, hypertension, and musculoskeletal disorders and in addition to this, it is also a risk factor for many varieties of cancer, including pancreatic, Non-Hodgkin's Lymphoma (NHL), colorectal, endometrial (the lining of the uterus), hepatocellular (subtype of liver cancer), kidney, cervical (adenocarcinoma of the cervix), esophagus (adenocarcinoma), thyroid, malignant melanoma (a type of skin cancer) (between males), gallbladder and post-menopausal breast cancers [2,4-7]. Besides, BMI of 30 or higher have shown critically high risk for myeloma and leukemia in dose-dependent manner [8]. Yet, it has been found in some studies that obesity is not associated with lymphoma and childhood cancers [9-11].

Cancer is currently the leading cause of death in developed countries and a second leading cause of death in developing countries [5,12-14]. Definition of cancer is an deviant growth of cells caused by multiple changes in gene expression leading to dysregulated balance of cell proliferation and cell death and ultimately evolving into a population of cells that can invade tissues and metastasize to distant sites, causing significant morbidity and, if untreated, death of the host [15].

There are a lot of evidence that support the relationship between adult obesity and overweight, and many cancers. Besides, the ascending epidemic of obesity and overweight precipitates more significant issues such as increasing amounts of new cancer cases and cancer deaths. Based on the research estimates, from the past (25 years ago) to present-day obesity precipitates approximately 14% of cancer deaths between males and up to 20% of cancer deaths between females [16,17]. In this

*Corresponding author: Melissa Kazan, Department of Nutrition & Dietetics, Yeditepe University, Istanbul-34000, Turkey, Tel: +90-507-836 16 04; E-mail: melissakazan666@gmail.com

way, these can be evaluated like the evidences of relationship between obesity and overweight, and many cancers. While individuals have increased substantial weight over this 25 years period, the prevalence of obesity and overweight has ascended from 15% in 1980 to 35% in 2005 [18,19] (Figure 1). Moreover, in terms of International Agency for Research on Cancer (IARC), the relation between obesity and overweight, and cancer was estimated and the outcomes were found like that obesity led to 39% of endometrial cancer cases, 37% of esophageal cancer cases, 25% of kidney cancer cases, 11% of colon cancer cases, and 9% of postmenopausal cancer cases in 2002, Europe [20]. Furthermore, according to the American Cancer Society estimates, deaths of pancreatic cancer, liver cancer, Non-Hodgkin's Lymphoma (NHL), and myeloma were relevant to obesity and overweight [16]. As a result, the World Cancer Research Fund, the International Agency for Research, and the American Institute for Cancer Research had found powerful evidences that have explained a cause and effect association between obesity and overweight, and inception of any cancers. Overall, while almost 20% of the whole cancer cases resulted from obesity and overweight, the combination of obesity and overweight (overnutrition or overeating) with diet had grown up to 25% of the risk ratio of whole cancer cases according to the research done by Wolin et al. Causes of cancer were given by help of Figure 2. At this figure, obesity and overweight was separated from diet and in addition, tobacco, alcohol, physical inactivity, viruses, occupation, pollution, sun & radiation, medication, family history, and reproductive factors were estimated and updated and figure was generated for the causes of cancer (Figure 2) [21-24].

The relations between obesity and cancer can be explained by variations in the metabolism of endogenous hormones (contain of insulin, insulin like growth factors and sex steroids) which may cause impairment of the normal balance between cell proliferation,

BMI (kg/m²)	WHO classification	Popular description
<18.5	Underweight	Thin
18.5-24.9	Normal range	"Healthy", normal or "acceptable" weight
25.0-29.9	Grade 1 overweight	Overweight
30.0-39.9	Grade 2 overweight	Obesity
≥40.0	Grade 3 overweight	Morbid obesity

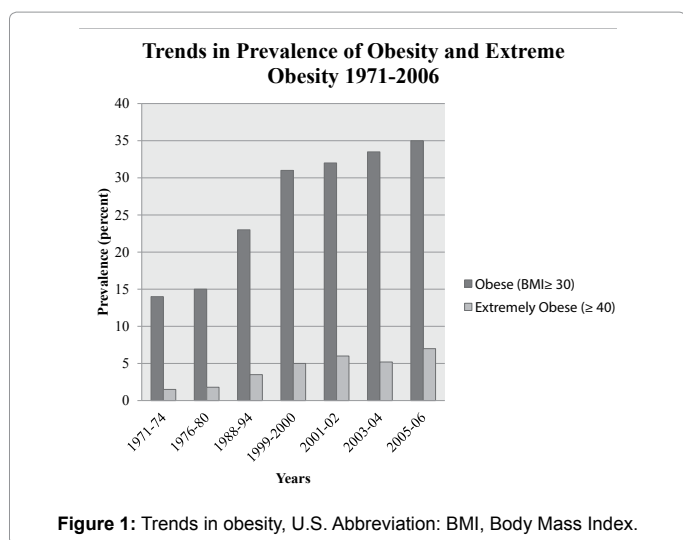**Table 1:** Cut points of BMI for the classification of weight.

Figure 1: Trends in obesity, U.S. Abbreviation: BMI, Body Mass Index.
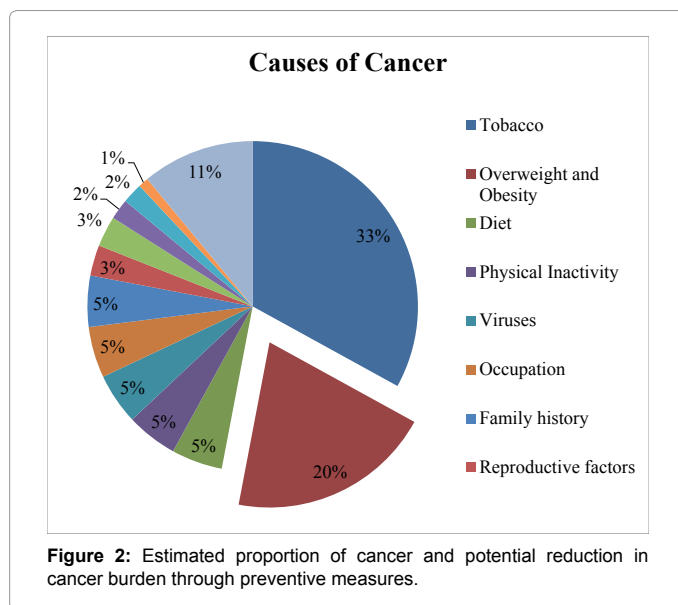

Figure 2: Estimated proportion of cancer and potential reduction in cancer burden through preventive measures.

differentiation and apoptosis. The reason is that, adipose tissue is considered as an active endocrine and metabolic "organ" through autocrine, endocrine and paracrine activities and eventually, different assumed biological mechanisms consisting of changes in the bioavailability and synthesis of sex steroid hormones, insulin resistance, release of growth factors and/or pro-inflammatory cytokines and deviant energy disposal and expenditure can cause progression and genesis of cancer [4,20]. In addition that, cancer genesis can indirectly be contributed to through a progressive aggregation of environmental chemical carcinogens in the adipose tissue by a modification of the hormonal milieu [11,20,25]. In this article, we review the different several types of cancer which have been associated with obesity/overweight.

Obesity and Esophageal Cancer

Esophageal cancer is the eighth most common cancer worldwide, responsible for 462,000 new cases in 2002 (4.2% of the total), and sixth most common cause of death from cancer with 386,000 deaths (5.7% of the total) [26-31]. Survival rates for esophageal cancer are poor: 16% of the patients in the United States [32] and 10% in Europe [33] survive at least five years [26]. In addition to this, in Europe in 2006, 34,300 men (2.0% of total cancer incidence in men) and 10 700 women (0.7% of total cancer incidence in women) were estimated and diagnosed with esophageal cancer newly. 29,300 men (3.1% of cancer deaths in men) and 9,200 women (1.2% of cancer deaths in women) died because of esophageal cancer in the same year [2,34]. Strikingly, according to research the highest risk country for esophageal cancer is China and the lowest risk country for esophageal cancer is western Africa [26,35,36] (Figure 3). Esophageal cancer occurs more common in males almost 3 fold higher than women in the World [2] and 7 fold higher than women in Eastern Europe [26]. However, in Asia and Africa the occurrence of esophageal cancer is much closer ratio between men and women [26].

There are the two main histological types of esophageal cancer. They include Esophageal Squamous Cell Carcinomas (ESCC or SCC) which basically take place in the upper and middle component of the esophagus, and Esophageal Adenocarcinomas (EAC or AC) which constantly originate from the lower component of the esophagus [37,38]. However, distal esophageal adenocarcinoma and gastro-esophageal junction and gastric cardiac adenocarcinoma are alike

in many ways so identification is frequently difficult [39]. While the prevalence of obesity has been increasing, the incidence of esophageal and gastric cardiac adenocarcinoma has been going up during previous decades but in contrast to this, the steady and even declined incidence of esophageal squamous cell carcinoma has been existing [20,39,40]. That is, increasing of adenocarcinomas is related to obesity but reverse association appears between esophageal squamous cell carcinoma and obesity [41,42].

Renehan et al., Reeves et al. and Samanic et al. studied cancers cases in men and women. They estimated of relative risks for cancer at different sites related to an increase in BMI of 10 kg/m² and risks for each site for overweight and obesity in the UK. According to meta-analysis in the 2008, relative risks for a 10 kg/m² increase in BMI for adenocarcinoma of the esophagus have been found 2.31 between men and 2.28 between women (95% CI 1.77-3.03 in men; 95% CI 1.72-3.03 in women) and the attributable risk for adenocarcinoma of the esophagus for a 10 kg/m² increase in BMI is approximately 40% in the UK (Table 2). However, relative risks for squamous cell carcinoma of the esophagus for a 10 kg/m² increase in BMI have been found 0.50 between males and 0.32 between females. In addition that, relative risks for squamous cell carcinoma of the esophagus for low BMI have been found 2.4 in men and 1.6 in women (95% CI 1.3-4.4 in men; 95% CI 0.5-4.8 in women for the highest quintiles) [41]. According to the research [43-46], the risk of squamous cell carcinoma has decreased with increased BMI subjects and it has been supported with results for Linxian and China. Nevertheless, some investigations have exhibited that the decrease was not important for the 2 highest quartiles of BMI [47-51]. As far as study in the UK [51], an important opposite relation between BMI and squamous cell carcinoma has been reported. However, an important decrease in risk was observed solely for the highest BMI interval (BMI 30, OR 0.28) [52]. That is, thin subjects have higher risk than obese subjects for squamous cell carcinoma of the esophagus. According to another research, Vaughan et al. in 1995, odds ratios for adenocarcinoma of the esophagus (examined 133 cases) and cancer of the gastric cardiac (examined 165 cases) for high BMI have been found 2.5 and 1.6 (95% CI 1.2-5.0 and 95% CI 0.8-3.0, respectively for the highest percentiles of BMI). Odds ratios for BMI above 25 kg/m²
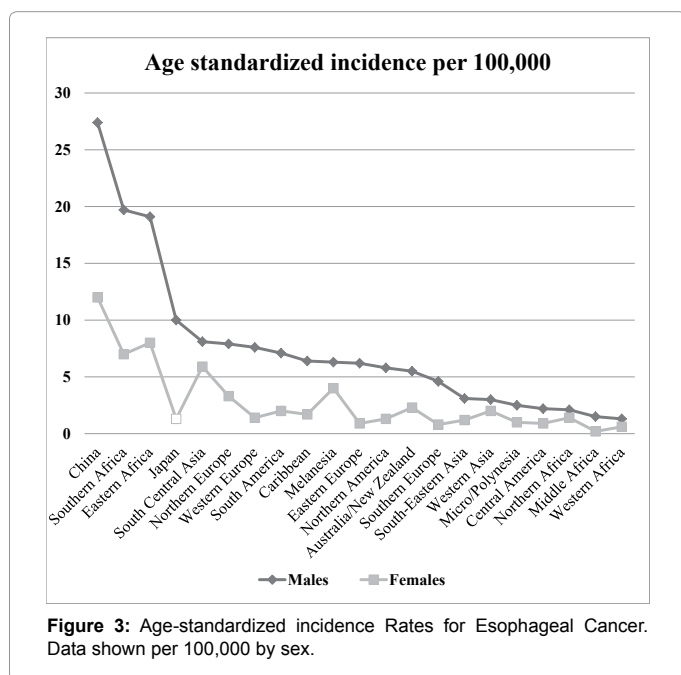
for adenocarcinoma of the cardiac have been reported 5.4 among men and 1.8 among women in Shanghai, China by Ji et al. in 1997 (95% CI 2.4-12.3 in males; 95% CI 0.5-6.4 in females). While odds ratios for the highest quartile of normal BMI for oesophageal adenocarcinoma have been reported 3.0 among men (95% CI 1.7-5.0) and 2.6 among women (95% CI 0.8-8.5) by Chow et al. in 1998, odds ratios for adenocarcinoma of the cardia were lower [20,41]. According to a quantitative meta-analysis included twelve case control studies and two cohort studies in 2002-2003, odds ratios for esophageal adenocarcinoma have been reported 1.8 for overweight in males (95% CI 1.5-2.2) and 2.4 for obese in men (95% CI 1.9-3.2) and 1.5 for overweight in females (95% CI 1.1-2.2) and 2.1 for obese in women (95% CI 1.4-3.2) comparing with usual-weight individuals were found in the analysis [2,53]. The odds ratios have been found 8.7 in non-smokers (95% CI 2.4-3.11) and 2.9 in current smokers (95% CI 1.1-7.6) for highest versus lowest quartiles of normal BMI [20]. In fact, squamous cell carcinoma of the esophagus has been strongly linked to both smoking and alcohol intake [2,38,41-45].

Obesity can cause esophageal cancer indirectly too. Obesity (abdominal obesity) [54] or high BMI leads to strongly gastro esophageal reflux disease (GERD or GORD), Gastro Esophageal Reflux Disease (GERD or GORD) can supports and develops the Barrett's Esophagus (BE) and progressed Barrett's Esophagus (BE) causes the esophageal adenoma and then esophageal adenocarcinoma respectively (Figure 4). There is a sequence reaction. Eventually, Gastro Esophageal Reflux Disease (GERD or GORD) and Barrett's Esophagus (BE) precipitates esophageal cancer along with obesity [20]. Moreover, obesity causes inflammatory esophagitis and finally esophageal adenocarcinoma is observed [2,30]. The exact role that obesity plays within these processes remains to be defined [2].

As result of these, the mechanism of adenocarcinoma of esophagus and the mechanism of squamous cell carcinoma of the esophagus is not completely comprehended but the causes of adenocarcinoma of esophagus seem like obesity, visceral and central obesity, esophageal reflux disease, Barrett's esophagus and esophagitis, and the causes of squamous cell carcinoma of the esophagus seem like low BMI, smoking and alcohol intake [30,54-56].

Obesity and Colorectal Cancer

Colorectal cancer is the second most common cancer in the developed countries. In the United States, it is estimated 56,290 deaths for colon cancer and rectum cancers in 2005 (approximately 10% of the total cancer deaths in the United States) and furthermore, 105,000 cases for colon cancer and 40,000 cases for rectum cancer were anticipated in 2005 [15]. In Europe, the researchers acquired the knowledge about new cases for colon cancer and rectum cancers in 2006. In accordance with this knowledge, the researchers diagnosed 217,400 new cases in men (12.8% of all cancer incidence between men) and 195,400 new cases in women (13.1% of all cancer incidence between women) for colon and rectum cancers. 107 600 in men (11.3% of total cancer deaths between men) and 99,900 in women (13.3% of total cancer deaths between women) died because of colorectal cancer in 2006 [34]. It was noticed that the second most widespread cause of cancer death was colorectal cancer in both men and women [57]. While approximately 1 million new cases (9.4% of the world total) for colon and rectum cancers were diagnosed in 2002, this amount, in 2002, increases over 1.2 million new cases for colorectal cancers in 2008. Besides, while the amount of death for colorectal cancer was almost 529,000 in 2002 that the amount was one half of new cases for colorectal cancer in 2002, the amount of death was estimated almost 608,700 for colorectal cancer in 2008 that it is the


Figure 3: Age-standardized incidence Rates for Esophageal Cancer. Data shown per 100,000 by sex.

Type of cancer	RR* per 10 kg/m² (for men)	95% CI (for men)	Attributable risk‡ (%) (for men)	RR* per 10 kg/m² (for women)	95 % CI (for women)	Attributable risk‡ (%) (for women)
Esophagus adenocarcinoma	2.31	1.77-3.03	40	2.28	1.72-3.03	37
Colon	1.54	1.44-1.64	22	1.19	1.10-1.28	8
Rectum	1.19	1.12-1.25	9	NS†	--	--
Gallbladder	NS†	--	--	2.53	1.04-6.10	41
Pancreas	NS†	--	--	1.25	1.04-1.49	11
Malignant melanoma	1.37	1.10-1.69	16	NS†	--	--
Breast postmenopausal	--	--	--	1.40	1.31-1.49	16
Endometrium	--	--	--	2.89	2.62-3.18	46
Ovary	--	--	--	1.14	1.03-1.27	6
Kidney	1.54	1.32-1.80	22	1.80	1.56-2.04	27
Thyroid	1.77	1.08-2.89	28	1.30	1.12-1.51	13
Non-Hongkin lymphoma	1.12	1.06-1.19	6	1.14	1.00-1.30	6
Multiple myeloma	1.23	1.10-1.39	11	1.23	1.14-1.32	10
Leukaemia	1.17	1.04-1.30	8	1.37	1.08-1.74	15
All cancers	1.10	1.04-1.15	5	1.12	1.09-1.14	6

Table 2: Estimates of the relative risks for cancer at different sites associated with an increase in BMI of 10 kg/m² and of the risks for each site for overweight and obesity in the UK.

*Estimates from Renehan et al. [42] except for breast, endometrium, ovary and all cancers in women from Reeves et al. [43] and all cancers in men taken as risk for BMI >30 kg/m² vs. BMI 18.5-24.9 kg/m² from Samanic et al. [44].

†As the association was not significant it was not reported.

‡Calculated using estimates of the prevalence of overweight and obesity in men and women aged 55-64 years in England in 2007 [45].

Figure 4: The association between obesity factor and oesophageal adenocarcinoma indirectly.
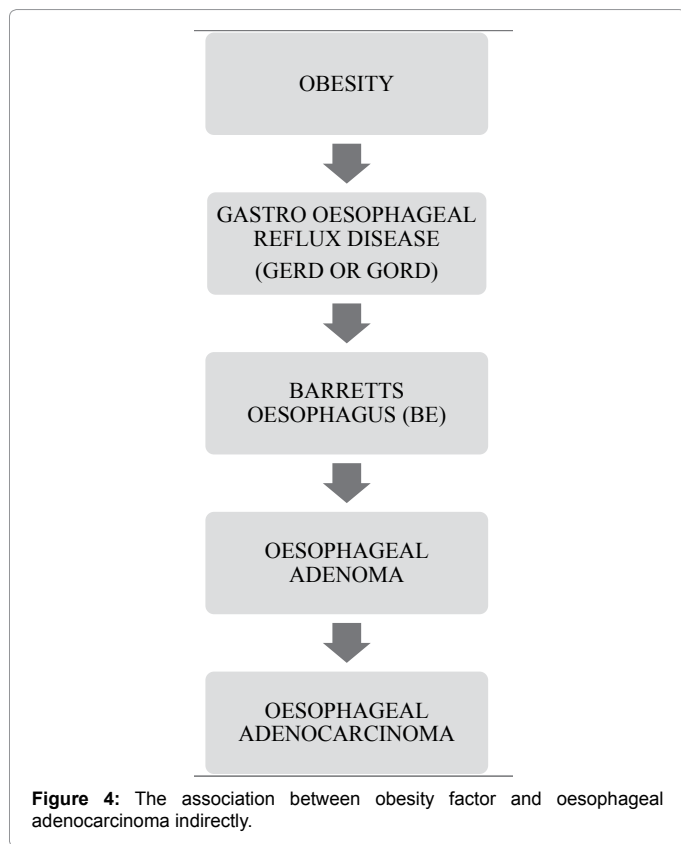
same pattern with 2002 (the one half of new cases for colorectal cancer in 2008). Ratio of diagnosed of colorectal cancer was the third among males and the second among females in 2008 during fourth between men and third between women in 2002 although the amounts were approximately the same between males and females in some countries (ratio, 1.2:1) [26,12]. Survival rate of colorectal cancer for males was estimated respectively from high ratio to low ratio between countries as following: 65% for North America, 54% for Western Europe, 34% for Eastern Europe, and 30% for India at five years. Whereas the highest incidence ratio for males was in Japan, females in Australia/New Zealand had the highest incidence ratio for colorectal cancer (Figure 5). In addition, according to the global cancer statistics in 2002 the highest incidence ratios were in Australia/New Zealand, in Japan and in Northern America and, the lowest incidence ratios were in Middle Africa and in South Central Asia for colorectal cancer (Figure 5) [26]. Data sets of the GLOBOCAN 2008 were almost the same with the global cancer statistics 2002. According to the GLOBOCAN 2008 the highest incidence ratios were in Europe, in Northern America and in Australia/New Zealand and, individuals in Africa and South Central Asia had the lowest ratios for colorectal cancer [12].

There are various reasons why individuals in different countries suffer from colorectal cancer. They are per capita consumption patterns of fiber, fat (especially animal fat), and meat [58-60]. Moreover, excessive body weight, a central accumulation of adiposity and immobile lifetime can alter the individual's risk ratio for colon cancer [61]. Also, according to the another research estimates, rising prevalence of smoking, ascending trend of obesity, and alterations in dietary patterns have changed individual's risk ratio for colon cancer both separately for each one and simultaneously for both conditions together [62-66]. Furthermore, the investigators had found changeable risk factors for colorectal cancer. They consist of immobile lifetime, overweight and obesity, severe alcohol consumption or alcoholism, red and processed meat consumption, and smoking [67-69]. Based on the research estimates, immigrations influence the risk ratio of colorectal cancer as well. The reasons of difference are environmental alterations that include dietary factor and the other environmental factors that form a main component of risk for colorectal cancer. For example,

Figure 5: Age-standardized incidence Rates for Colorectal Cancer. Data shown per 100,000 by sex.
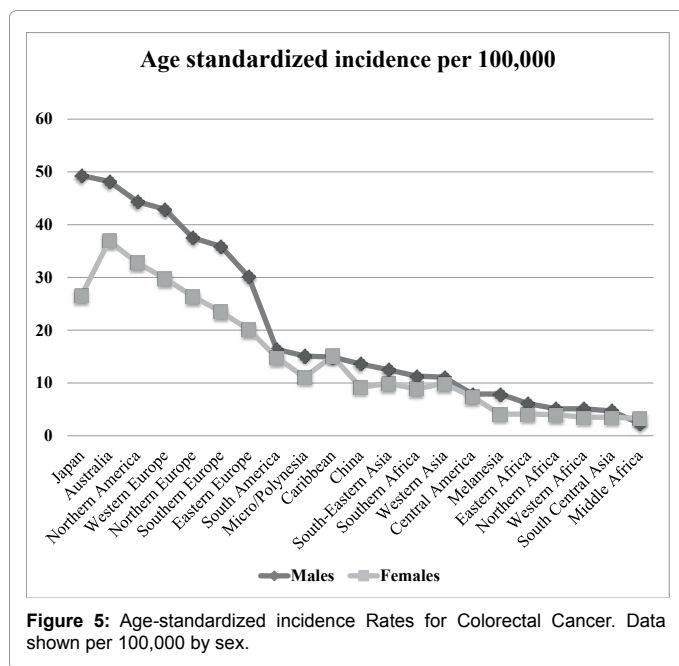
Japanese individuals born and living in the United States possess higher risk ratios of colorectal cancer than those of United States Whites (38.4 per 100,000 between males, and 27.6 per 100,000 between females). In addition to this, it was observed that Japanese individuals born and living in Los Angeles possess higher risk ratios for colorectal cancer as well (48.0 per 100,000 between males, and 32.8 per 100,000 between females) and the ratios in Japanese individuals born and living in Hawaii are 51.2 per 100,000 between males, and 30.8 per 100,000 between females [70-72].

All the consequences of these evidences demonstrate us a common ground between obesity and colorectal cancer. In 2002-2003 report of World Health Organization (WHO) and the International Agency for on Cancer has explained that obesity and overweight enhances the risk ratio of colorectal cancer [7]. However, there is a difference between females and males. Increased BMI raises the risk ratio of colon cancer higher in males than in females [2,20,42]. According to meta-analysis in the 2008, the relative risk for a 10 kg/m² increase in BMI for colon cancer has been found 1.54 among males (95% CI 1.44-1.64 in men). However, the relative risk for colon cancer for a 10 kg/m² increase in BMI has been found 1.19 among females (95% CI 1.10-1.28 in women). The attributable risk for colon cancer for a 10 kg/m² increase in BMI is approximately 22% between Englishmen and attributable risk for colon cancer among Englishwomen is 8%. In addition to this, based on the same research estimates the relative risk for rectum cancer has been found 1.19 between men for a 10 kg/m² increase in BMI (95% CI 1.12-1.25 among males) and the attributable risk for rectum cancer is 9% among males for a 10 kg/m² increase in BMI. In contrast to men, significant association in women has not been found between increased BMI and rectum cancer (Table 2) [41,42]. In terms of the eight case control investigations, the relative risks for colorectal cancer have been reported higher between overweight (BMI ≥25 kg/m²] and obese (BMI ≥30 kg/m²] people than normal weight people (BMI 18.5-24.9 kg/m²]. In contrast to this, one study has been reported no association among colorectal cancer risk and BMI and even, another study has been reported an adverse association among colorectal cancer risk and BMI between women. According to the ten prospective cohort studies about colorectal cancer and BMI, a positive relation has been found and

reported in all of these and also, the relative risks for the ten prospective cohort studies have been recorded in the interval from 1.2 to 3.4. As a result, the association between colorectal cancer and obesity has been demonstrated powerfully but the relation between colon cancer and obesity has more significant than the relation between obesity and rectum cancer and also, the distal colon has more powerful association than the proximal colon. Moreover, according to seven epidemiological investigations, the association between BMI and colorectal adenoma has been found and even, increased BMI has caused especially large adenomas of the distal colo-rectum. In fact, visceral or abdominal obesity has more significant than BMI for colorectal cancer risk. In particular waist circumference and Waist to Hip Ratio (WHR) are both used for the diagnosis of abdominal obesity (or central obesity). In this way, waist circumference and Waist to Hip Ratio (WHR) give to evaluate the relation of between obesity and colorectal cancer more reliable information than BMI, particularly among older people.

Based on the investigation estimates, a high Waist to Hip Ratio (WHR) has influenced the risk ratio of colon cancer and it has increased the risk ratio to a 2.1 fold for colon cancer between males contrasting the high waist to hip ratio to those with the low waist to hip ratio, whereas the high body mass index (BMI >29.2 kg/m²) has increased the risk ratio to a 1.7 fold for colon cancer contrast to the low body mass index (BMI <24.8 kg/m²]. Additionally, according to the other large prospective investigation about BMI and colorectal cancer, it had been found and recorded that the high waist measurement (waist size >99.1 cm) has ascended the risk ratio for colorectal cancer to a 2 fold between males and females contrast to the low waist measurement (waist size <83.8 cm) [73-78]. Furthermore, between obese premenopausal women obesity has led to increase greater in colorectal cancer risk than obese postmenopausal women. Based on the Million Women Study estimates, the relative risks of colorectal cancer for a 10 kg/m² increase in BMI have been recorded as 1.16 between premenopausal women (95% CI 1.05-2.48 in premenopausal women) and 0.99 between postmenopausal women (95% CI 0.88-1.12 in postmenopausal women) [41,43].

There are a lot of reasons that obesity increases the risk ratio of colorectal cancer. We can say that obesity change stable equilibrium and in this way, derangement of energy homeostasis occur and then this dys-regulation is related to colorectal carcinogenesis [78]. However, it is obvious that there is a difference of relative risk ratio for colorectal cancer between females and males. The reason is that while men and women gain weight, fat accumulation occur different areas of the body and further, they own distinct body compositions. Body fat percentage for females is higher and the quantity is approximately 30%, whereas fat percentage of whole body for males is approximately 20%. Additionally, fat distribution in males become too much abdominal region and it is denominated as abdominal obesity or central obesity, or apple shaped, as to women fat accumulation become too much around the hips and it is denominated as gluteofemoral obesity or gynecoid, or peripheral obesity, or pear-shaped. Indeed, it has been shown that abdominal obesity associates with metabolic abnormities more strongly than gluteofemoral obesity. Therefore, in women abdominal fat accumulation can be more significant marker for colon cancer risk than BMI and body weight. Also European Prospective Investigation into Cancer and Nutrition (EPIC) has supported this hypothesis. According to EPIC, abdominal obesity, diagnosed with waist to hip ratio or waist circumference, is an equally influential risk factor of colon cancer between males and females, whereas BMI and body weight are related to colon cancer risk among males but not among females [2,79]. In addition, EPIC has found one proof about that abdominal obesity

is an equally influential risk factor of colon cancer between males and females rather than total obesity. This proof was plasma levels of C-peptide. C-peptides are breakdown products that are appeared when the pancreatic hormone insulin is generated and released. Moreover, C-peptide measurements are tightly associated with visceral fat aggregation. Hence, C-peptide measurements have been indicated to be correlatively strongly concerned with the risk of colon cancer between males and females [80]. Oppositely, EPIC has reported that the anthropometric measurements and plasma levels of C-peptide were not significantly associated with rectal cancer, and even total obesity and abdominal obesity also do not influence substantially the risk of rectal cancer [79,80].

The association between abdominal obesity and colon cancer can be explained that obesity leads to increased plasma insulin levels (or insulin resistance) and other dysregulated mechanisms (Figure 6). Significantly, the researchers have said for the association between obesity and colon cancer that the essential mechanism is insulin resistance or the impaired ability to standardize plasma glucose levels. Insulin is known being multifunctional hormone which one is the growth promoting effect, and information from various sources assert that insulin is involved functionally in colorectal carcinogenesis. According to the research estimates, it has also supported that individuals suffered from type 2 diabetes (T2DM), is a chronic disease that appears when insulin resistance occurs at the same time with impaired insulin secretion, have increased risk ratio of colon cancer and additionally positive association between C-peptide levels and plasma insulin and risk of colon cancer has been found. Initially, insulin resistance causes hyperglycemia, hyperinsulinaemia, and elevated levels of fatty acids.

Raised concentrations of insulin can stimulate a mitogenic activity within colonocytes, whereas heightened concentrations of fatty acids and glucose can cause variations in cell signaling pathways, metabolic perturbations and oxidative stress. Researchers said with regard to strong evidences that hyperinsulinaemia is the direct pathway from the adiposity to colon cancer. Actually, hyperinsulinaemia is associated with elevated levels of Insulin like Growth Factor-1 (IGF-1), which is known to promote cancer. Insulin influences with the IGF-1 axis by decreasing the synthesis of IGF-1 binding proteins (IGFBP), thus ascending the bioavailability of IGF-1. According to the observational and experimental studies done, IGF-1 can increase the development of colorectal cancer. In the liver increased IGF-1 activity prevents hepatic sex hormone binding globulin synthesis and after increased levels of sex hormones like estrogen and testosterone is observed. Additionally, IGF-1 and insulin induce sex hormone synthesis by the adrenal glands and gonads. Due to alterations in the sex hormone levels, the effect of obesity can become different between men and women. The association between obesity and colorectal cancer risk was not found among females, because high estrogen levels can resist the adverse effect of obesity through insulin pathways. Based on the recent investigation suggest, adipose tissue derived cytokines and hormones, unitedly termed adipokines, can also be involved in production of new tumors (tumourigenesis), including leptin, that stimulates growth of epithelial cells in colon, and adiponectin, that has antitumor and antiangiogenic activities. Low levels of adipocyte derived hormone adiponectin developed with obesity enable increased tumourigenesis and angiogenesis. However, the accurate role of the adipokines remains to be described for the risk of colon cancer. The chronic inflammation exists in the pathogenesis of obesity and recently its importance has been highlighted and moreover it can present an additional mechanism contacting elevated adiposity to colo-rectal carcinogenesis [2,41,78].

As result of these, the mechanism of colon cancer is not completely comprehended but nevertheless there is a relation between colon cancer and obesity. However, strong evidences have not been found to support the association between obesity and rectal cancer yet.

Obesity and Breast Cancer

Breast cancer is the second most commonly diagnosed cancer worldwide, responsible for 1.15 million new cases in 2002, and fifth most common cause of death from cancer, and moreover the first cause of cancer death in females according to the research in 2002 (the 411,000 yearly deaths exhibit 14% of cancer deaths in women). Besides, investigators asserted prognosis for breast cancer in 2002, and breast cancer with 4.4 million survivors (17.9% prevalence for breast cancer) is the most prevalent cancer worldwide (until 5 years following diagnosis). Also, between women the most common cancer is breast cancer (23% of the total cancer) [26]. In 2006, investigators diagnosed 429,900 new cases for breast cancer in Europe, and they explained that the most frequent cancer is breast cancer not only between females (28.9% of the whole woman incident cancers), but also between all European individuals. Likewise, in 2006 the most common reason for cancer mortality among females is breast cancer with 131,900 deaths (17.9% of the whole cancer deaths among females) in Europe [34]. In accordance with GLOBOCAN 2008, the most commonly diagnosed cancer (approximately 1.38 million) and cause of cancer mortality among women (approximately 458,400) is breast cancer in economically developing and developed countries (responsible for 23% of all new cancer cases, and 14% of all cancer mortalities respectively) [12].

According to research done in 2002, industrialized countries had higher amounts of the cases, with reference to these approximately 361,000 cases in Europe (27.3% of cancers between females) and approximately 230,000 cases in North America (31.3% of cancers between females). Most of the developed countries except for Japan had high incidence ratios and the highest incidence ratio by far was in Northern America, in 2002 (99.4 age standardized incidence per 100,000) (Figure 7) [26]. More moderate incidence ratios for breast cancer in 2002 were in South America, Eastern Europe, Western Asia, Micro/Polynesia, and Southern Africa but until now change relevant to incidence ratios for breast cancer among females has not happened in these geographic areas. Most regions of Africa (within Western, Northern, Eastern, and Middle Africa areas) and most areas of Asia (the exception of Western Asia) had the low incidence ratios (<30 age standardized incidence per 100,000) for breast cancer in 2002. The lowest incidence ratio for breast cancer was in Middle Africa, 2002
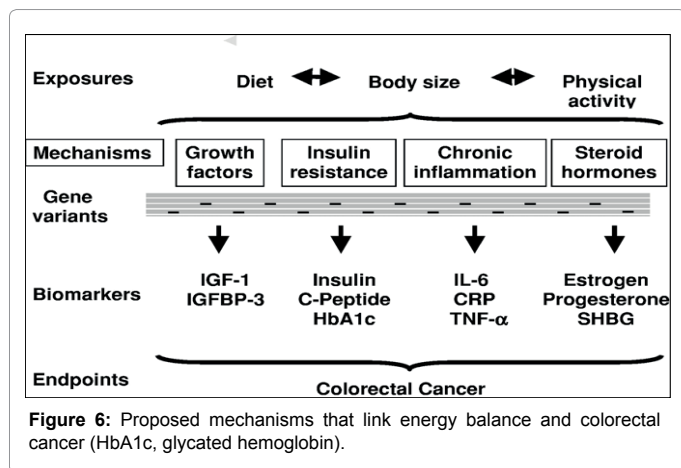

Figure 6: Proposed mechanisms that link energy balance and colorectal cancer (HbA1c, glycated hemoglobin).

(16.5 age standardized incidence per 100,000) [26].

The prognosis for breast cancer was clarified by researchers and estimated survival ratios were 73% in the developed countries and 57% in the developing countries. The highest survival ratio for breast cancer cases was in United States (81%). Despite huge differences of survival ratios for breast cancer between countries, mortality ratios for breast cancer between countries were approximately the same (Figure 7). For example, while the mortality ratio for breast cancer was 19.2% in Northern America (it had the highest incidence ratio for breast cancer), the mortality ratio of breast cancer was 12.1% in Middle Africa (it had the lowest incidence ratio for breast cancer). Generally, the ratios for breast cancer mortality were approximately between 22.6 and 5.5. Due to high incidence and low mortality of breast cancer, it is the most prevalent type of cancer worldwide today and will be similar to that in the future [26].

The association between breast cancer risk and obesity has been investigated in manifold studies. Complicated outcomes have obtained from these studies taken together [2]. Generally, it has been reported that inverse relative risk between breast cancer and obesity or high BMI has been found among individuals under the age of 49, whereas positive relative risk between breast cancer and obesity or high BMI has been reported among individuals over the age of 80 years. A lot of studies like this indicated that menopausal status may be a significant determinant in the effect of obesity or high BMI on risk of breast cancer [81]. The concern between anthropometric measures and premenopausal and post-menopausal breast cancers is summed up in Table 3 and will be examined in the present review [81].

Basically, while positive association have been found between risk of breast cancer and high BMI or obesity in post-menopausal females, contrary relations have been found between premenopausal females [2,81]. The relative risk for post-menopausal breast cancer has been found to be 1.26 (95% CI 1.09-1.46) among individuals who have had a high BMI (>28 kg/m²] contrasted with individuals who have had a low BMI (<21 kg/m²] [81]. Based on the information from the Pooling Project, the relative risk for breast cancer increased up to 1.3 (95% CI

Figure 7: Age-standardized Incidence and Mortality Rates for Prostate Cancer. Data shown per 100,000.

	Premenopausal breast cancer risk	Postmenopausal breast cancer risk
Weight	-	++
BMI	-	++
Central fat deposition	+	++

Table 3: Anthropometric measurements and associated risk for premenopausal and postmenopausal breast cancer. +: increased risk; -: decreased risk.

1.1-1-5) among individual who have had above a BMI of 20 kg/m² and up to BMI of 28 kg/m², and further did not increase [20]. Risk for breast cancer with BMI above 27 kg/m² has been expressed to be 10-60% elevated risk for breast cancer in many general studies, but a more than two fold increased risk has been found in some other general studies [20]. However, a reduction associated with obesity for breast cancer risk has been found between premenopausal females [41].

The relative risk ratio for breast cancer for a 10 kg/m² increase in BMI has been reported to be 0.86 between premenopausal females by the Million Women Study researchers [43], and the meta-analysis done in 2008 have presented approximately similar results [42]. Information from another study has been explained that the risk for breast cancer was recorded to be 0.54 (95% CI 0.34-0.95) between females had a great BMI (above 31 kg/m²] contrasted with females had a low BMI (below 21 kg/m²] [81]. Previous studies (the Pooling Project, the Nurses' Health Study and the Women's Health Initiative) have also supported identical results [2]. Besides, the risk for breast cancer has decreased approximately 18% among premenopausal females had the high amount of BMI (>25-28 kg/m²] contrasted with premenopausal females had the low amount of BMI (<21 kg/m²] [2,82]. Eventually, there is an important inverse relation between premenopausal breast cancer and BMI [81].

Also, the association between risk of breast cancer and high BMI or obesity among post-menopausal females not used Hormone Replacement Therapy (HRT) has been expressed to be stronger contrasted with females used Hormone Replacement Therapy (HRT). That is, females not used HRT have had higher association between obesity and breast cancer risk than females used HRT, and even no evidence with regard to this subject has been found between females used HRT [2,20,41,82].

For example, according to the EPIC studies, the relative risk ratio for breast cancer between post-menopausal females who have had the high BMI (>25 kg/m²] contrasted with the low BMI (<21 kg/m²] was explained to be 1.36 (95% CI 1.06-1.75) between non hormone replacement therapy users, while important associations were not found between HRT users [82]. Besides, the relative risk ratio for breast cancer for a 10 kg/m² increase in BMI has been reported to be 1.40 between post-menopausal females not used hormone replacement therapy by the Million Women Study researchers (Table 2) [41,43]. Based on the research done in the UK, the attributable risk for breast cancers between post-menopausal females not used hormone replacement therapy has been found approximately 16% for a 10 kg/m² increase in BMI (Table 2) [41]. Information from another study has been reported that females not used HTR had 1.6 increased risk for breast cancer [20]. Furthermore, according to the EPIC study, between post-menopausal females who had not used HTR and had gotten over 20 kg through adulthood (from age of 20 to age of 60 years), the risk for post-menopausal breast cancer was increased to 52% approximately contrasted with individuals who had stayed with stable weight through adulthood [2].

The mechanism between breast cancer risk and obesity has not been completely understood, but nevertheless we can summarize some reported hypothesis in Table 4. Association between breast
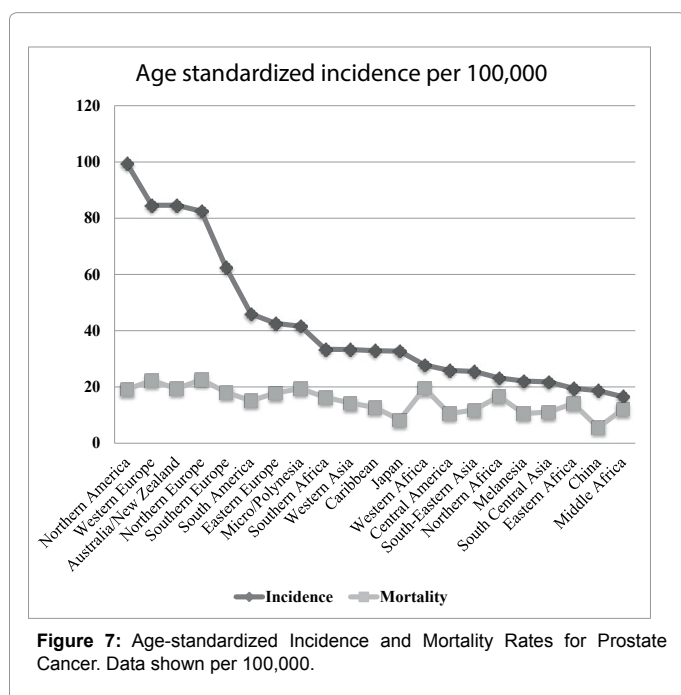
Mechanisms
Reduced detection of tumour, late diagnosis
Increased free bioactive oestrogen levels*
Increased androgen levels*
Increased extra-glandular conversion of androgens to oestrogens
Decreased steroid hormone binding globulin
Increased growth factors (i.e. insulin-like growth factor*)
Increased receptors for growth factors
Decreased specific binding proteins for growth factors
Hyper-insulinaemia
Increased insulin resistance
Elevated non-esterified fatty acids
Increased lipid-soluble carcinogens, especially in the breast*

Table 4: Possible mechanisms involved with obesity and breast cancer risk. *Mechanisms with direct involvement in mammary carcinogenesis.

cancer risk and obesity include several mechanisms such as cytokines, growth factors, insulin and sex hormones [2] (especially estrogens mediate increased risk of breast cancer together with obesity between post-menopausal females presumably [41]]. Obesity causes hyperinsulinaemia that is associated to decreased synthesis of Insulin Like Growth Factor Binding Protein-1 and 2 (IGFBP-1 and 2) and as a result of that elevated levels of insulin like growth factor-1 (IGF-1) [2,83]. Both IGF-1 and insulin can promote cancer by inhibiting apoptosis and increasing cell proliferation [84]. Moreover, increased IGF-1 activity prevents hepatic secretion of sex hormone binding globulin and after increase levels of sex hormones like testosterone and estradiol between post-menopausal obese females [2,41,81,83], eventually inhibited apoptosis and increased cell proliferation happen by binding to androgen and estrogen receptors.

Besides hyperinsulinaemia also directly affects hepatic sex binding globulin synthesis [2,81,83]. Breast cancer between post-menopausal females is positively associated to levels of free testosterone and estradiol in plasma [7,85], and it can be said that elevated levels of estrogens and especially elevated levels of estradiol may largely explain the relation among breast cancer risk and obesity in post-menopausal females [2,7,8,20,41]. The adipose tissue generates aromatase (is an enzyme that metabolizes sex steroids) that converts androgenic precursors from the gonads and adrenal into estradiol and estrogen (are precursors of estrogens) in fat cells [2,8,41]. Between post-menopausal females estrogen production in ovarian is stopped, and the fundamental site of endogenous estradiol and estrogen is adipose tissue between post-menopausal females [2,8]. In this way, obese post-menopausal females have higher (approximately 2-fold) concentrations of sex hormones (e.g. oestradiols) in circulation than thin post females [2,41]. It is the main reason that obesity in post-menopausal females causes breast cancer [8]. However, between users of hormone replacement therapy no association has been observed among obesity and breast cancer risk because the main reason for breast cancer is endogenous estrogen production [20]. Unlike post-menopausal obese females, between premenopausal obese females decreased levels of sex steroid hormones in circulation occurs through presence of anovulatoric cycles (are related to obesity) and thus an inverse association between premenopausal breast cancer and high BMI or obesity can be reported [2,41]. More recent investigations present that leptin and adiponectin (adipose tissue derived hormones) can also directly contribute to progress of breast cancer [2]. We can summarize these mechanisms in Figures 8 and 9.
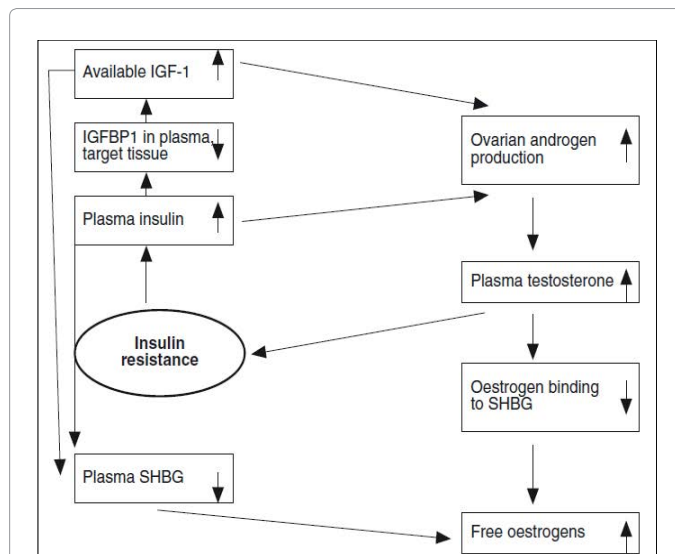

Figure 8: The role of insulin resistance in the development of a hyperandrogenic endocrine profile. IGF-1, insulin-like growth factor-1; IGFBP1, insulin-like growth factor binding protein 1; SHBG: Sex Hormone-binding globulin (adapted from Kaaks, 1996).
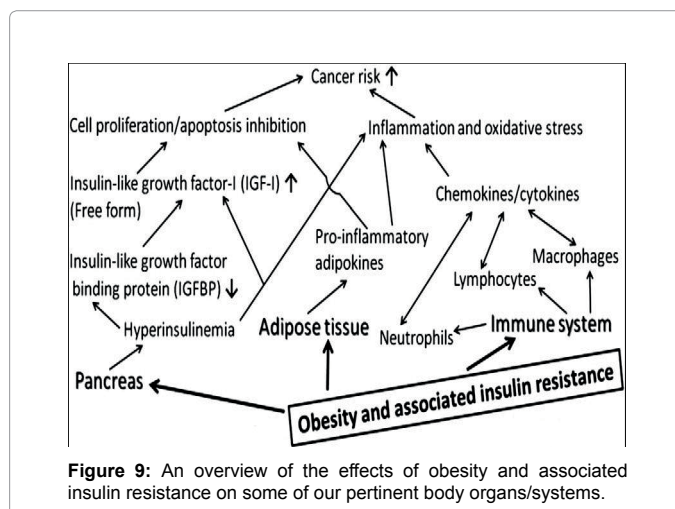

Figure 9: An overview of the effects of obesity and associated insulin resistance on some of our pertinent body organs/systems.

As result of these, the mechanism of breast cancer for post-menopausal females is not completely comprehended but the causes of post-menopausal breast cancer seem like insulin resistance, multiple metabolic and hormonal changes, hyperinsulinaemia, increased androgen levels, conversion of androgen to estrogen in adipose tissue, and decreased levels of SHBG related to obesity [81], and the causes of inverse relation between obesity and premenopausal breast cancer seem like anovular menstrual cycle and lower levels of sex steroid hormones [41]. A significant point should be considered that obesity between premenopausal females is probably to cause obesity through life and thus to an ultimate increase of breast cancer risk [20,41].

Obesity and Endometrial Cancer

Association between obesity and endometrial cancer (the lining of the uterus) has been evaluated in the manifold investigations. According to the Million Women Study, the relative risk for endometrial carcinoma for a 10 kg/m² increment of BMI has been found to be 2.89 (1.77 between premenopausal females and 3.98 between post-

menopausal females) and the attributable risk for endometrial cancer for a 10 kg/m² increment of BMI has been found to be approximately 46% between post-menopausal females in the UK (Table 2) [41]. In the one study, the attributable risk for endometrial cancer for an increase in weight of five kilogram has been recorded to be approximately 13%. In the other case control investigation, it has been found that the relative risk for endometrial cancer is 2.0 (95% CI 1.2-3.3) between females who have high BMI (>30 kg/m²] contrasted to individuals who have low BMI (<23 kg/m²] [20].

Based on the EPIC Study estimates, the relative risks for endometrial cancer have been reported to be 1.78 (95% CI 1.41-2.26) between obese individuals and to be 3.02 (95% CI 1.66-5.52) between morbid obese individuals (BMI ≥40 kg/m²] contrasted to normal weight individuals. Oppositely, the relative risk for endometrial cancer has been reported to be 1.11 (95% CI 0.91-1.36) between overweight females in the same investigation [2]. According to the investigations, generally old obese females have higher risk ratio for endometrial cancer than young obese females. Distinctively, in one study, increase in the risk ratio for endometrial cancer has been reported to be similar between young and old obese females. In the other investigation, the risk ratio for endometrial cancer with obesity has been found to be stronger between premenopausal females. Nevertheless, it has been said that obesity in late adulthood appeared stronger association with endometrial cancer than obesity in early age of individuals [20].

Also, assessment of adiposity can give a better consequence to be associated with endometrial cancer risk than BMI. Adiposity can measure using with a lot of different techniques such as WHR (waist hip ratio), hip or waist circumference, and sub scapular skin fold. These measurements have been all reported to be importantly and positively related to endometrial cancer risk in some of investigations. However, in some investigations, WHR (waist hip ratio) has not been remained related to endometrial cancer after arrangement of BMI. In the three investigations, WHR has been independently related to endometrial cancer risk but in the three investigations, after arrangement of BMI, this relationship has lost its importance. Moreover, sub scapular skin fold can give better result to evaluate endometrial cancer risk than waist hip ratio yet it become expressionless to evaluate endometrial cancer risk after arrangement of BMI [2,20]. In some of investigations, after arrangement of BMI, only the relative risk for endometrial cancer for high waist circumference (≥ 88 cm) contrasted to low ones (<80 cm) has remained important that its value was 1.50 (95% CI 1.10-2.04) [2] and it has been found that evaluating abdominal body fat for endometrial cancer risk have more concerned contrasted to gluteofemoral body fat [2,20].

In addition that, the association between risk of endometrial cancer and high BMI or obesity and waist and hip circumference among females not used Hormone Replacement Therapy (HRT) has been expressed to be stronger contrasted to females used Hormone Replacement Therapy (HRT). That is, females not used HRT have had higher association between obesity and breast cancer risk than females used HRT, and even no evidence with regard to this subject has been found between females used HRT [2].

Consequently, in the most investigations, it has been found that obesity or high BMI has increased endometrial cancer risk. However, in some investigations, it has been found that the elevated risk has been represented only for the highest risk interval of BMI. Therefore, the mechanism between endometrial cancer risk and obesity has not been completely understood [20]. Nevertheless, we can say some reported hypothesis. This hypothesis is approximately the same with hypothesis

of breast cancer. Accordingly, between premenopausal obese females, obesity causes increased continuous anovulation and as a result of this, elevated ovarian androgen production and subsequently lack of progesterone.

Eventually, elevated exposure to estradiol (is precursor of estrogens) occurs by lack of progesterone. This mechanism has been called the 'unopposed estrogen' hypothesis that the mitogenic effects of estrogens can precipitate to develop endometrial cancer. Between post-menopausal obese women, high weight causes insulin resistance and hyperinsulinaemia that is associated with decreased synthesis of Insulin like Growth Factor Binding Protein-1 (IGFBP-1) and as a result of that elevated levels of Insulin like Growth Factor-1 (IGF-1). Both IGF-1 and insulin can promote cancer by inhibiting apoptosis and increasing cell proliferation. Moreover, increased IGF-1 activity prevents hepatic secretion of sex hormone binding globulin and after increase levels of serum concentration of estradiol and specific androgens between post-menopausal obese females, eventually inhibited apoptosis and increased cell proliferation happen by binding to androgen and estrogen receptors. Consequently, high level of estrogens and low level of progesterone (arises the absence of ovarian progesterone synthesis) can lead to endometrial cancer. Besides, high estrogen can lead to increase IGF-1 synthesis in endometrial tissue and low progesterone can lead to decrease IGFBP-1 synthesis and subsequently formation of endometrial tumor [2,41].

We can summarize these mechanisms in Figure 10. As result of these, the mechanism of endometrial cancer for obese females is not completely comprehended but yet, we can say finally that endometrial cancer can be associated with increased plasma insulin levels, elevated IGF-1 synthesis, reduced IGFBP-1 synthesis, low plasma SHBG levels, increased plasma estrogens and androgens and low plasma progesterone levels (Table 5) [2,41].

Obesity and Other Types of Cancer

Investigators have said that other types of cancer can also be related to obesity, in spite of limited data that does not enable to definite consequences [2].
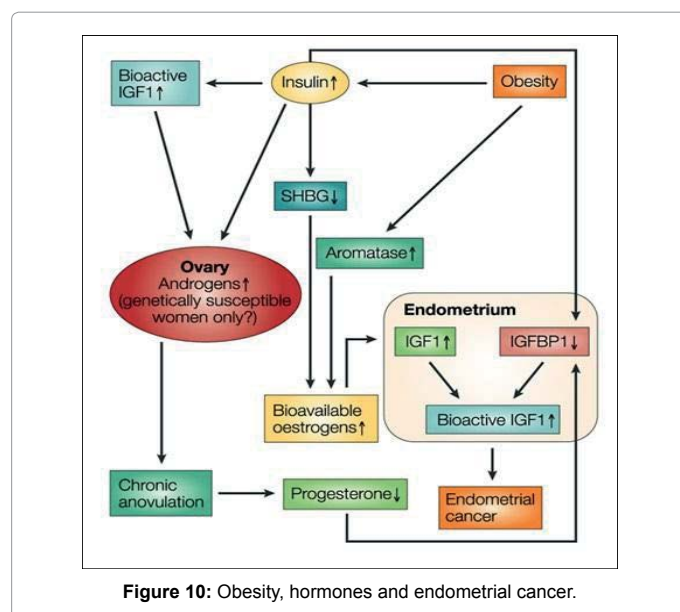

Figure 10: Obesity, hormones and endometrial cancer.

Mechanisms
Increased plasma insulin levels
Elevated IGF-1 synthesis
Reduced IGFBP-1 synthesis
Low plasma SHBG levels
Increased plasma estrogens and androgens
Low plasma progesterone levels

Table 5: Possible mechanisms related to obesity and endometrial cancer risk.

Obesity and renal cancer

Association between obesity and renal cancer has been evaluated in the manifold investigations. The risk for renal cancer has been reported to be 2.6-fold elevated by associating with the highest quartile of BMI contrasted with the lowest. According to pooled four of the case control studies, the risk for renal cell cancer has been reported to be 3.6-fold elevated between females and 1.6-fold elevated between males by associating with the fourth quartile of BMI contrasted with the first [20]. In the 2008 meta-analysis, the relative risk for kidney carcinoma for a 10 kg/m² increase in BMI has been reported to be 1.54 among males and 1.80 among females and the attributable risk for renal cell carcinoma for a 10 kg/m² increase in BMI is approximately 22% between men and 27% between women in the UK (Table 2) [41]. As well as all these studies, according to the eleven case control studies, between either females or males an elevated risk ratio for renal cell cancer was reported by relating to increased BMI and based on the nine case control studies, we can say that between both males and females an elevated risk ratio for renal cell cancer was reported by relating to high BMI [20]. According to the European Prospective Investigation into Cancer (EPIC), there is an association between high BMI and renal cancer risk in females, but not in males. Even, the relative risk for renal cell carcinoma has been reported to be approximately 1.68 between females (95% CI 1.03-2.75) who had high BMI (≥30 kg/m²) contrasted to those with normal BMI (<25 kg/m²) and to be approximately 1.06 between males (95% CI 0.66-1.70) who had high BMI (≥30 kg/m²) contrasted to those with normal BMI (<25 kg/m²) [2].

The international collected investigation and four case control investigations have indicated that the risk ratio for renal cell carcinoma has been elevated greater between females than between males by associating with increased BMI [2,20]. Furthermore, one investigation has indicated that the risk ratio for renal cell carcinoma has been elevated equally between both males and females by relating to high BMI [2]. However, one case control investigation has showed an inverse result that the risk ratio for renal cell carcinoma has been elevated greater between men than between women by relating to increased BMI [20]. Oppositely, according to another investigation, association between renal cancer and obesity has not been found among both females and males. In addition, it has been examined by researchers that whether there is an association between cancer of the renal pelvis (rare type of the cancer) and BMI or not and as a result of this, any relation has not been found [20].

As a result, it was established in the most of investigations that obesity and overweight (or high BMI) increases the risk of renal cell carcinoma. However, the biological mechanism for renal cell carcinoma associated with obesity has not been completely understood [2,41]. In addition, the differences between men and women in the relative risk (generally more high in females than in males) have not been exactly explained. While some researcher had said that hormonal levels and gender specific fat distribution lead to these differences, others had said that body fat distribution does not guess the risk of renal cell

carcinoma [2,20]. Besides, renal cell carcinoma risk in obese individual has increased independently of high blood pressure [20]. That is, we can understand that different mechanisms of high blood pressure (or hypertension) and obesity (or high BMI) may separately influence kidney cancer [20,41]. At the same time, a risk factor for renal cell carcinoma is hypertension that is strongly related to high BMI (or obesity) [41].

Obesity and pancreatic cancer

Investigators has been reported some inconsistencies between the risk of pancreas cancer and obesity or overweight. In 2002, it has been reported that obesity does not lead to pancreas cancer in the IARC report. However, in 2007, persuasive evidences associated with obesity and pancreas cancer has been found by the World Cancer Research Fund investigators. In 2008, UK, whereas it has been found that the relative risk ratio for pancreas cancer for a 10 kg/m² elevated in BMI was 1.25 between females, no important association has been found between males (Table 2). In the same study, the attributable risk between pancreas cancer and obesity and overweight has been found to be approximately 11% between females (Table 2) [41]. According to the twenty one independent prospective investigations, the relative risk for pancreatic cancer for 5 kg/m² increase of BMI has been reported to be 1.16 (95% CI 1.05-1.28) between males and to be 1.10 (95% CI 1.02-1.19) between females [2].

The mechanism between obesity and pancreas cancer has not been understood completely. Diabetes (arises because of obesity) can be associated with elevated risk of pancreatic cancer yet it is unclear [41].

Obesity and Ovarian Cancer

Association between obesity and ovarian cancer has been evaluated in the manifold investigations. According to some of them, the association has been found between obesity and ovarian cancer, but in other investigation researchers have found no correlation between obesity and ovarian cancer [2,20]. According to the twenty eight studies, the risk for ovarian cancer has been reported to be 1.2 fold elevated (95% CI 1.0-1.3) by associating with overweight and to be 1.3 fold elevated (95% CI 1.1-1.5) by associating with obesity [2]. However, opposite consequences has been found in a lot of cohort studies. In 1994, no association between obesity and ovarian cancer was found among obese females contrasted with Danish individuals by Moller et al. In addition, again in 1994 (Törnberg and Carstensen), no increased risk (relative risk=1.0; 95% CI 0.92-1.1) for ovarian cancer between Swedish females was found by associating with BMI. In another study, relative risk between BMI and ovarian cancer was reported to be 1.1 (95% CI 0.64-1.9). According to the case control studies, a direct association was found in five investigations, no association was found in four investigations and an inverse association was found in one investigation [20].

In a conclusion, inconsistent reports about ovarian cancer and obesity do not allow any outcome to be defined the association. That is, no relation was found with obesity [20].

Conclusions

Obesity importantly causes a lot of types of cancer such as adenocarcinoma of esophagus, colorectal cancer, endometrial cancer (the lining of the uterus), post-menopausal breast cancer and renal cell cancer [41]. Furthermore, obesity can lead to elevate other cancer risk the kind of gallbladder cancer, pancreatic cancer, hepatocellular cancer (subtype of liver cancer), thyroid cancer, cervical cancer (adenocarcinoma of the cervix), Non-Hodgkin Lymphoma (NHL),

leukemia, multiple myeloma and malignant melanoma (a type of skin cancer). We have multiple adequate evidences about that. Nevertheless, the mechanisms between cancer risk and obesity are uncertain for a lot of cancer types [2]. Besides, obesity affects higher levels on endometrial cancer (the attributable risk is 46%) and adenocarcinoma of the oesophagus (the attributable risks are 40% between males and 37% between females) than on other (Table 2). In addition, current investigations assert that the attributable risks for all cancers are approximately 5% between males and 6% between females by associating with obesity and overweight in the UK (Table 2). Consequently, it is assumed that obesity affects differently on cancer sites [41].

Most of investigations present association between obesity and cancer in separately males and females due to differences of their body composition and body fat distribution. Nevertheless, gender specific outcomes do not exhibit in many researches. Moreover, in most of investigations, degree of adiposity (or obesity) was determined with using BMI. However, body fat distribution cannot be evaluated by using BMI. Hence, degree of adiposity and determine of obesity should be found by using combination of varied measurement techniques (like waist circumference, BMI, waist hip ratio) in the future investigations. Also, it is uncertain whether or not a linear association exists between cancer risk and body fat accumulation and whether or not there is a threshold value. As a result, the mechanism between cancer risk and obesity should be investigated in depth in the future researches [2], and if the increase of obesity rates will continue, an elevated prevalence of cancer will be seen in the future [41].

References

1. (1998) Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 158: 1855-1867.

2. Pischon T, Nothligs U, Boeing H (2008) Obesity and Cancer in the Symposium on Diet and Cancer. Proceedings of the Nutrition Society 67: 128-145.

3. WHO Expert Committee on Physical Status. Physical status: the use and interpretation of anthropometry. Geneva: WHO; 2002.

4. Irigaray P, Newby JA, Lacomme S, Belpomme D (2007) Overweight/obesity and cancer genesis: more than a biological link. Biomed Pharmacother 61: 665-678.

5. Louie SM, Roberts LS, Nomura DK (2013) Mechanisms linking obesity and cancer. Biochim Biophys Acta 1831: 1499-1508.

6. Bianchini F, Kaaks R, Vainio H (2002) Overweight, obesity, and cancer risk. Lancet Oncol 3: 565-574.

7. Joint World Health Organization/Food and Agriculture Organization Expert Consultation. 2003. Diet, Nutrition and the Prevention of Chronic Diseases. WHO Technical Report Series no. 916. Geneva: WHO.

8. Lichtman MA (2010) Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. Oncologist 15: 1083-1101.

9. Willett EV, Skibola CF, Adamson P, Skibola DR, Morgan GJ, et al. (2005) Non-Hodgkin's lymphoma, obesity and energy homeostasis polymorphisms. Br J Cancer 93: 811-816.

10. Uauy R, Solomons N (2005) Diet, nutrition, and the life-course approach to cancer prevention. J Nutr 135: 2934S-2945S.

11. Irigaray P, Newby JA, Clapp R, Hardell L, Howard V, et al. (2007) Lifestyle-related factors and environmental agents causing cancer: an overview. Biomed Pharmacother 61: 640-658.

12. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.

13. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62: 10-29.

14. Vucenik I, Stains JP (2012) Obesity and cancer risk: evidence, mechanisms, and recommendations. Ann N Y Acad Sci 1271: 37-43.

15. Raymond W. Ruddon, Cancer Biology 2007. University of Michigan Medical School Ann Arbor, Michigan. Fourth edition.

16. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348: 1625-1638.

17. Wolin KY, Carson K, Colditz GA (2010) Obesity and cancer. Oncologist 15: 556-565.

18. Flegal KM, Carroll MD, Ogden CL, Johnson CL (2002) Prevalence and trends in obesity among US adults, 1999-2000. JAMA 288: 1723-1727.

19. www.cdc.gov (Feb 2015).

20. IARC: Weight Control and Physical Activity. IARC Handbooks of Cancer Prevention, vol 6. Lyon: Iarc Press; 2002.

21. Colditz GA, Wolin KY, Gehlert S (2012) Applying what we know to accelerate cancer prevention. Sci Transl Med 4: 127rv4.

22. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371: 569-578.

23. Freedland SJ, Platz EA (2007) Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev 29: 88-97.

24. Doll R, Peto R (1981) The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 66: 1191-1308.

25. Irigaray P, Ogier V, Jacquenet S, Notet V, Sibille P, et al. (2006) Benzo [a] pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice: a novel molecular mechanism of toxicity for a common food pollutant. FEBS J 273: 1362e72.

26. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108.

27. Mao WM, Zheng WH, Ling ZQ (2011) Epidemiologic risk factors for esophageal cancer development. Asian Pac J Cancer Prev 12: 2461-2466.

28. Enzinger PC, Mayer RJ (2003) Esophageal cancer. N Engl J Med 349: 2241-2252.

29. Zhang Y (2013) Epidemiology of esophageal cancer. World J Gastroenterol 19: 5598-5606.

30. Long E, Beales IL (2014) The role of obesity in oesophageal cancer development. Therap Adv Gastroenterol 7: 247-268.

31. Ryan AM, Duong M, Healy L, Ryan SA, Parekh N, et al. (2011) Obesity, metabolic syndrome and esophageal adenocarcinoma: Epidemiology, etiology and new targets. Cancer Epidemiology 35: 309-319.

32. Ries LAG, Eisner MP, Kosary CL (2004) SEER cancer statistics review, 1975-2001. Bethesda, MD: National Cancer Institute; 2004. Available at: http://seer.cancer.gov/csr/1975_2001/. Accessed December 2, 2004.

33. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, et al. (2003) EUROCARE-3: survival of cancer patients diagnosed 1990-94--results and commentary. Ann Oncol 14(5): v61-118.

34. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, et al. (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18: 581-592.

35. Ferlay J, Bray, F, Pisani, P, Parkin DM (2002) GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide; IARC Press: Lyon, France, 2004.

36. Melhado RE, Alderson D, Tucker O (2010) The changing face of esophageal cancer. Cancers (Basel) 2: 1379-1404.

37. Chandrasoma P, Wickramasinghe K, Ma Y, DeMeester T (2007) Adenocarcinomas of the distal esophagus and "gastric cardia" are predominantly esophageal carcinomas. Am J Surg Pathol 31: 569-575.

38. Munoz N, Day NE (1996) Esophageal cancer. In: Schottenfeld D, Fraumeni JF (eds.) Cancer Epidemiology and Prevention, (2ndedn) Oxford: Oxford University Press, pp. 681-706.

39. Brown LM, Devesa SS (2002) Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am 11: 235-256.

40. Pera M, Manterola C, Vidal O, Grande L (2005) Epidemiology of esophageal adenocarcinoma. J Surg Oncol 92: 151-159.

41. Key TJ, Spencer EA, Reeves GK (2010) Symposium 1: Overnutrition: consequences and solutions. Obesity and cancer risk. Proc Nutr Soc 69: 86-90.

42. Reeves GK, Pirie K, Beral V, Green J, Spencer E, et al. (2007) Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 335: 1134.

43. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr (2006) Relation of body mass index to cancer risk in 36,552 Swedish men. Cancer Causes Control 17: 901-909.

44. The Information Centre for Health and Social Care (2009) Statistics on obesity, physical activity and diet: England, February 2009. http://www.ic.nhs.uk/statistics-and-datacollections/health-and-lifestyles/obesity/ statistics-on-obesity-physical-activity-and-diet:-england-february-2009 (accessed June 2009).

45. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, et al. (1998) Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 90: 150-155.

46. Blot WJ, McLaughlin JK (1999) The changing epidemiology of esophageal cancer. Semin Oncol 26: 2-8.

47. Crew KD, Neugut AI (2004) Epidemiology of upper gastrointestinal malignancies. Semin Oncol 31: 450-464.

48. Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, et al. (2005) Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer 113: 456-463.

49. Lindblad M, Rodríguez LA, Lagergren J (2005) Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 16: 285-294.

50. Kubo A, Corley DA (2006) Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 15: 872-878.

51. Holmes RS, Vaughan TL (2006) Epidemiology and Pathogenesis of Esophageal Cancer. 1053-4296/06/$-see front matter ©2006 Elsevier Inc. All rights reserved. doi: 10.1016/j.semradonc.2006.09.003.

52. Crowell MD, Bradley A, Hansel S, Dionisio P, Kim HJ, et al. (2009) Obesity is associated with increased 48-h esophageal acid exposure in patients with symptomatic gastroesophageal reflux. Am J Gastroenterol 104: 553-559.

53. Lagergren J, Bergström R, Lindgren A, Nyrén O (1999) Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340: 825-831.

54. Boyle P, Ferlay J (2005) Mortality and survival in breast and colorectal cancer. Nat Clin Pract Oncol 2: 424-425.

55. Armstrong B, Doll R (1975) Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 15: 617-631.

56. Prentice RL, Sheppard L (1990) Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Control 1: 81-97.

57. McKeown-Eyssen G (1994) Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev 3: 687-695.

58. Giovannucci E (2002) Modifiable risk factors for colon cancer. Gastroenterol Clin North Am 31: 925-943.

59. Center MM, Jemal A, Ward E (2009) International trends in colorectal cancer incidence rates. Cancer Epidemiol Biomarkers Prev 18: 1688-1694.

60. Center MM, Jemal A, Smith RA, Ward E (2009) Worldwide variations in colorectal cancer. CA Cancer J Clin 59: 366-378.

61. García-Alvarez A, Serra-Majem L, Ribas-Barba L, Castell C, Foz M, et al. (2007) Obesity and overweight trends in Catalonia, Spain (1992-2003): gender and socio-economic determinants. Public Health Nutr 10: 1368-1378.

62. Martín JJ, Hernández LS, Gonzalez MG, Mendez CP, Rey Galán C, et al. (2008) Trends in childhood and adolescent obesity prevalence in Oviedo (Asturias, Spain) 1992-2006. Acta Paediatr 97: 955-958.

63. de Kok IM, Wong CS, Chia KS, Sim X, Tan CS, et al. (2008) Gender differences in the trend of colorectal cancer incidence in Singapore, 1968-2002. Int J Colorectal Dis 23: 461-467.

64. Ferrari P, Jenab M, Norat T (2007) Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer 121: 2065-2072.

65. Giovannucci E, Wu K (2006) Cancers of the colon and rectum. In: Schottenfeld D, Fraumeni JF Jr (eds.) Cancer Epidemiology and Prevention. New York: Oxford University Press, pp. 809-829.

66. Boyle P, Levin B (2008) World Cancer Report 2008. Lyon, France: World Health Organization. International Agency for Research on Cancer.

67. McMichael AJ, McCall MG, Hartshorne JM, Woodings TL (1980) Patterns of gastro-intestinal cancer in European migrants to Australia: the role of dietary change. Int J Cancer 25: 431-437.

68. Kolonel LN, Hinds MW, Hankin JH (1980) Cancer Patterns among Migrant and Native-born Japanese in Hawaii in Relation to Smoking, Drinking and Dietary Habits. In: Gelboin HV, MacMahon B, Matsushima T (eds). Genetic and Environmental factors in Experimental and Human Cancer. Tokyo, Japan: Japan Scientific Societies Press, pp. 327-340.

69. Parkin DM, Whelan SL, Ferlay J (2002) Cancer Incidence in Five Continents. Vol. VIII, IARC Scientific Publications No. 155. Lyon, France: International Agency for Research on Cancer.

70. Boutron-Ruault MC, Senesse P, Méance S, Belghiti C, Faivre J (2001) Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. Nutr Cancer 39: 50-57.

71. Lin J, Zhang SM, Cook NR, Rexrode KM, Lee IM, et al. (2004) Body mass index and risk of colorectal cancer in women (United States). Cancer Causes Control 15: 581-589.

72. Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, et al. (2004) A prospective study of body size and colon cancer mortality in Japan: The JACC Study. Int J Obes Relat Metab Disord 28: 551-558.

73. Moore LL, Bradlee ML, Singer MR, Splansky GL, Proctor MH, et al. (2004) BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord 28: 559-567.

74. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertig DM, et al. (2004) Body size and composition and colon cancer risk in men. Cancer Epidemiol Biomarkers Prev 13: 553-559.

75. Gunter MJ, Leitzmann MF (2006) Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes. Journal of Nutritional Biochemistry 17: 145-156.

76. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, et al. (2006) Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 98: 920-931.

77. Jenab M, Riboli E, Cleveland RJ, Norat T, Rinaldi S, et al. (2007) Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 121: 368-376.

78. Lovegrove JA (2002) Obesity, body fat distribution and breast cancer. Nutr Res Rev 15: 389-412.

79. Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT, et al. (2004) Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer 111: 762-771.

80. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4: 579-591.

81. Sandhu MS, Dunger DB, Giovannucci EL (2002) Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 94: 972-980.

82. Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PH, et al. (2005) Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr Relat Cancer 12: 1071-1082.

83. Potischman N, Swanson CA, Siiteri P, Hoover RN (1996) Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. J Natl Cancer Inst 88: 756-758.

84. Tworoger SS, Eliassen AH, Kelesidis T, Colditz GA, Willett WC, et al. (2007) Plasma adiponectin concentrations and risk of incident breast cancer. J Clin Endocrinol Metab 92: 1510-1516.

85. Ray A, Cleary MP (2012) Obesity and breast cancer: a clinical biochemistry perspective. Clin Biochem 45: 189-197.