Metabolism Clinical and Experimental 92 (2019) 136–146

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Burden of cancer attributable to obesity, type 2 diabetes and associated risk factors

Alejandro López-Suárez

Hospital Virgen del Camino, carretera de Chipiona km 0.64, 11540 Sanlúcar de Barrameda, Cádiz, Spain

ARTICLE INFO

Article history:
Received 31 August 2018
Received in revised form 23 October 2018
Accepted 28 October 2018

ABSTRACT

Overweight and obesity constitute a global pandemic with devastating consequences that affect >2 billion people. Obesity plays a central role in morbidity and mortality of diseases of multiple organs and systems, and it is a major contributor to the growing incidence of cancer. There is now sufficient level of evidence for the association between overweight and 11 types of cancer, among which are two of the most common cancers worldwide, those of the colorectum and postmenopausal breast. Sedentary lifestyle, unhealthy diet, and excessive alcohol intake also account for the burden of cancer by promoting obesity. The risk of specific types of cancer is also directly influenced, regardless of the magnitude of adiposity, by physical inactivity, consumption of red meat, processed meat and ultra-processed foods, dairy products, alcohol, whole grain cereals, nuts, vegetables, and fruits. Type 2 diabetes is another global health threat closely associated with obesity that boosts the risk of cancer driven by high BMI. Education to promote positive choices and physical activity and resolute public health interventions on food delivery are requested to reduce the burden of obesity-related cancer and lighten the unsustainable growing expenses to health systems.

Contents

Abbreviations: BMI, Body mass index; CVD, Cardiovascular Disease; IARC, International Agency for Research on Cancer; IGFs, Insulin growth factors; OECD, Organization for Economic Co-operation and Development; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

E-mail address: a.lopez.ssl@gmail.com.

https://doi.org/10.1016/j.metabol.2018.10.013
0026-0495/

1. Introduction

Overweight and obesity have become a global pandemic with devastating consequences, accounting for the third highest global social burden after tobacco and armed violence [1]. In 2015, 19.5% of the population across the countries of the Organization for Economic Co-operation and Development (OECD) was obese. However, in countries such as New Zealand, Mexico and the United States (US), these figures exceeded 30% [2]. Obesity plays a central role in the morbidity and mortality of diseases affecting the cardiovascular, respiratory, and musculoskeletal systems, and it is one of the main promoters of type 2 diabetes, high blood pressure, and dyslipidaemia. Obesity is also a major contributor to the growing incidence of cancer that may overtake tobacco as the leading preventable cause of cancer [3,4]. Of particular importance is the association of overweight with breast and colorectal cancer, two of the most common cancers worldwide. By 2008, medical expenditures related to obesity were estimated at $147 billion in the US and $1.5 trillion per year worldwide [1,5]. Aside from quitting smoking, there are very few isolated interventions capable of achieving an impact on human health and reducing expenses, such as the prevention of overweight and obesity.

This manuscript summarizes the best evidence published in the last two decades about the risk of cancer associated with obesity and its related risk factors, including type 2 diabetes. This is not a systematic review of all research about obesity and cancer. The information in this manuscript summarizes that provided for international agencies and societies such as the World Health Organization, the International Agency for Research on Cancer (IARC), the American Society of Clinical Oncology, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), and the Centers for Disease Control and Prevention. It also includes evidence from the most prominent research based on systematic reviews, meta-analyses, and large prospective studies released after 2015, the last year covered by the position papers of the IARC and the WCRF/AICR. Special emphasis has been paid to highlight the areas of concordance and disparities between different publications. Putative mechanisms of oncogenic transformation in obesity and type 2 diabetes, and the effects of intentional weight loss on cancer incidence are also reviewed.

2. Prevalence of Overweight and Obesity

Overweight and obesity are the abnormal or excessive accumulation of fat. They are estimated most commonly by the body mass index (BMI), although it does not discriminate the percent of body fat or the body distribution of adiposity. In adults, a BMI of 25.0 to 29.9 kg/m^2 is considered overweight, and 30.0 kg/m^2 or more is considered obesity.

During recent decades, the global prevalence of a BMI of 25 kg/m^2 or greater has risen by 27% in adults and 47% in children. This means an increase in the number of overweight and obese people from 900 million in 1980 to 2 billion in 2013, and the OECD projections foresee a steady increase over the next two decades [6]. In Europe, overweight and obesity accounted for up to 53% of the adult population in 2014 [7]. The range of prevalence varied from 10% in Italy and Switzerland to >25% in the United Kingdom and Hungary (Fig. 1) [2]. In Asia, despite the growing incidence of obesity in very populated regions of China and India, available data up to 2013 indicate a relatively low prevalence of obesity at approximately 4% in men and women. However, China and India were within the 10 countries that accounted for more than half of obese people worldwide in 2013 [6].

3. Risk of Cancer in Overweight and Obese People

Cases of cancers not related to overweight and obesity have decreased during the first two decades of this century. However, the cases of cancer related to overweight and obesity have increased [8]. In 2012, it was estimated that 3.6% of all cancers worldwide in adults were attributable to high BMI. Of these, endometrial, postmenopausal breast, and colon cancers accounted for 63.6% of all cases. Every increase of BMI by 5% has been associated with a 10% greater risk of death related to cancer. In 2014, overweight and obesity-related cancers accounted for up to 40% of all cancers (55% in women and 24% in men) [9,10]. The most remarkable increase was for endometrial, ovarian, and postmenopausal breast cancers [8]. With the exception of postmenopausal breast cancer, an increase in BMI during childhood, adolescence, and young adulthood confers a similar risk to that in adulthood. In contrast, the absence of body adiposity throughout life lowers the risk of most cancers [11]. Overweight- and obesity-related cancers are more frequent in people over 50 years old, in women, in non-Hispanic black people, and in more developed countries [8,12].

In 2018, the WCRF/AICR released an extensive systematic review from 514 studies and meta-analyses published through 2015, with a level of evidence that links overweight and obesity to the risk of specific types of cancer of different localizations [13]. Also in 2018, the IARC advanced its conclusions about the cancer-preventive effects of the absence of excess body adiposity based on studies and meta-analyses published through 2015, which will be published in the upcoming Volume 16 of the IARC Handbooks of Cancer Prevention [11,14]. The WCRF/AICR and the IARC Working Group classified the strength of the evidence differently, and whereas the WCRF/AICR makes public health recommendations based on the level of evidence, the IARC Working Group does not provide recommendations.

The WCRF/AICR and the IARC agree about that there is convincing and sufficient evidence linking overweight and an increased risk of cancers of the oesophagus (adenocarcinoma), colon and rectum, liver, pancreas, postmenopausal breast, endometrium, and renal adenocarcinoma. The WCRF/AICR assigned a lower level of evidence than that assigned by the IARC for cancers of the gastric cardia, gallbladder, and ovary. The WCRF/AICR also found some level of evidence for cancers that had not been addressed by the IARC, such as cancers of the mouth, pharynx and larynx, cervix, and premenopausal breast. In this last case, overweight would confer a probable protective effect (Table 1). According to the WCRF/AICR, there is concordance among the different methods of assessment of adiposity, such as BMI, waist circumference, and waist to hip ratio [13].

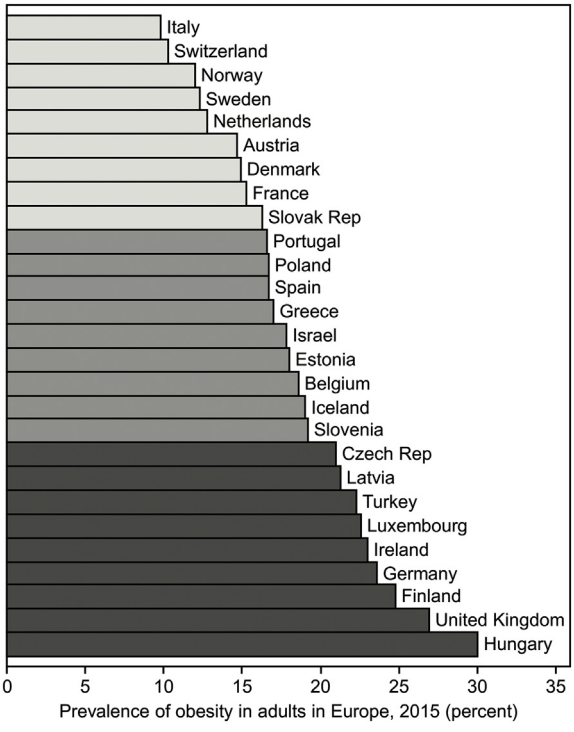

Fig. 1. Prevalence of obesity in adults in Europe, 2015.

Table 1
Strength of the evidence of the risk of cancer for overweight and obesity according to the criteria of the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).

Cancer site	IARC Working Group[a]		WCRF-AICR[b]	
	Level of evidence	RR (95% CI)[c]	Level of evidence	RR (95% CI)[c,d]
Oesophageal adenocarcinoma	Sufficient	4.8 (3.0–7.7)	Convincing	1.48 (1.35–1.62)
Gastric cardia	Sufficient	1.8 (1.3–2.5)	Probable	1.23 (1.07–1.40)
Colon and rectum	Sufficient	1.3 (1.3–1.4)	Convincing	1.05 (1.03–1.07)
Liver	Sufficient	1.8 (1.6–2.1)	Convincing	1.30 (1.16–1.46)
Gallbladder	Sufficient	1.3 (1.2–1.4)	Probable	1.25 (1.15–1.37)
Pancreas	Sufficient	1.5 (1.2–1.8)	Convincing	1.10 (1.07–1.14)
Post-menopausal breast	Sufficient	1.1 (1.1–1.2)[c]	Convincing	1.12 (1.09–1.15)
Endometrium	Sufficient	7.1 (6.3–8.1)	Convincing	1.50 (1.42–1.59)
Ovary	Sufficient	1.1 (1.1–1.2)	Probable	1.06 (1.02–1.11)
Renal adenocarcinoma	Sufficient	1.8 (1.7–1.9)	Convincing	1.30 (1.25–1.35)
Meningioma	Sufficient	1.5 (1.3–1.8)	NA	NA
Thyroid	Sufficient	1.1 (1.0–1.1)[c]	NA	NA
Multiple myeloma	Sufficient	1.5 (1.2–2.0)	NA	NA
Male breast	Limited	NA	NA	NA
Fatal prostate cancer	Limited	NA	Probable	1.08 (1.04–1.12)
Diffuse large B-cell lymphoma	Limited	NA	NA	NA
Oesophageal squamous-cell	Inadequate	NA	NA	NA
Gastric non-cardia	Inadequate	NA	NA	NA
Extrahepatic biliary tract	Inadequate	NA	NA	NA
Lung	Inadequate	NA	NA	NA
Cutaneous melanoma	Inadequate	NA	NA	NA
Testis	Inadequate	NA	NA	NA
Urinary bladder	Inadequate	NA	NA	NA
Brain or spinal cord glioma	Inadequate	NA	NA	NA
Mouth, pharynx and larynx	NA	NA	Probable	1.15 (1.06–1.24)
Cervix	NA	NA	Limited-suggestive	1.02 (0.97–1.07)
Pre-menopausal breast	NA	NA	Probable[e]	0.93 (0.90–0.97)

NA, not available.
[a] The IARC assigned the strength of the evidence for a cancer-preventive effect of the absence of excess body fatness as sufficient, limited or inadequate.
[b] The WCRF/AICR assigned the strength of evidence for the risk of cancer for the excess of body fatness as convincing, probable, and limited but suggestive.
[c] Relative Risk (95% confidence interval) of the highest vs. normal body mass index category.
[d] Relative Risk per 5 body mass index units.
[e] Probable reduction of risk.

Numerous individual studies and meta-analyses of specific types of cancers have been released since 2015. An umbrella review of systematic reviews and 204 meta-analyses evaluated the association between different indices of adiposity and risk of developing or dying from cancer [15]. Their results support the vast majority of the conclusions of the WCRF/AICR and IARC Working Groups. In 12 meta-analyses, the level of evidence was judged to be strong for cancers of oesophagus (adenocarcinoma), colorectum in men, biliary tract system, pancreas, postmenopausal breast, endometrium, kidney, and multiple myeloma. In 17 meta-analyses, the level of evidence was highly suggestive of colon, liver, postmenopausal breast, endometrium, and kidney cancer. The level of evidence was suggestive in 23 meta-analyses for cancer of colorectum, pancreas, ovary, prostate (mortality), thyroid, non-Hodgkin lymphoma, multiple myeloma, and leukaemia. In 19 meta-analyses, it was weak for cancer of oesophagus (adenocarcinoma), melanoma, endometrium, ovary, prostate (advanced), thyroid, non-Hodgkin lymphoma (mortality), and leukaemia.

4. Type 2 Diabetes and Cancer

Diabetes has become one of the most worrisome global health problems in this century. It is estimated that 425 million people worldwide have diabetes, which accounts for over 8.8% of the population aged 20–79 years, with an attributed total healthcare expenditures estimated to be $727 billion in 2017 [16]. Type 2 diabetes is closely associated with obesity, which shares common risk factors and comorbidities. Weight loss through intensive lifestyle interventions of diet and physical activity accounts for most of the preventive effects on new cases of diabetes [17]. In patients already diagnosed with diabetes, the level of cardiorespiratory fitness is associated with mortality from cancer [18].

An umbrella review of 18 meta-analyses published through 2013 has assessed the risk of developing cancer in type 2 diabetes patients [19]. Of 20 different cancer sites, the following four types were linked with type 2 diabetes with a robust level of evidence and without evidence of bias: breast (RR 1.20; 95% CI, 1.12–1.28), colorectum (RR 1.27; 95% CI, 1.21–1.34), intrahepatic cholangiocarcinoma (RR 1.97; 95% CI, 1.57–2.45), and endometrium (RR 1.97; 95% CI, 1.71–2.27). In 2017, a pooled analysis of 19 cohort studies included in the Asia Cohort Consortium found a positive association between diabetes and cancer of the breast, colorectum, bile ducts, and endometrium. Other cancer sites significantly associated with diabetes were liver, gallbladder, pancreas, ovary, prostate, kidney, and thyroid [20].

In 2018, an extensive analysis of the worldwide risk of cancer related to diabetes provided information about the population attributable fraction for 12 cancers in 175 countries using data from the GLOBOCAN Project of the IARC [21]. Diabetes and high BMI combined were responsible for 5.6% of all 14,067,894 new cases of cancer worldwide. Of them, 2.0% were attributable to diabetes, and 3.9% were attributable to high BMI. In women, 147,400 new breast cancer cases constituted 29.7% of all cancers attributable to diabetes and high BMI, and 121,700 endometrial cancer cases constituted 24.5% of all new cancers. In men, 126,700 cases of liver cancer, and 63,200 cases of colorectal cancer comprise 42.8 and 21.4% of all new cancer cases attributable to diabetes and high BMI, respectively. Countries from East and Southeast Asia deserve special mention, as these regions supported the second largest proportion of cases of cancer worldwide attributable to overweight and diabetes after high-income western countries in 2012. Of particular importance were the cases of liver cancer, which contributed 53.8% to the total cancer burden related to overweight and diabetes [21].

5. Physical Activity and Cancer

Energy expenditure is essential for weight loss and to maintain a healthy weight. A minimum level of moderate intensity physical activity of at least 150 min per week is recommended. Muscular strength, global cardiorespiratory fitness status, and sedentary leisure time are also determinants of energy expenditure and influence the risk of cancer.

5.1. Physical Activity and Cardiorespiratory Fitness

Physical activity of only moderate intensity is associated with a substantial reduction in total mortality, cardiovascular mortality, and cancer-related mortality, with a favourable dose-response from the minimum level to a level as high as 10 times greater without evidence of harm [22,23]. Pooled data from 12 prospective cohort studies, comprising 1.44 million participants from Europe and the US, with a median follow-up period of 11 years, provided strong evidence on the association between leisure-time physical activity and cancer incidence. A high level of physical activity was associated with a lower risk of 10 types of cancers independent of BMI, including the three most common cancers worldwide, i.e., cancers of the lung, breast, and colon and rectum (Table 2). High levels of physical activity were also positively associated with non-advanced prostate cancer and melanoma, possibly as a consequence of greater exposure to sunlight [24]. Although a high level of physical activity does not eliminate the risk of cancer and death associated with obesity, it is beneficial at any level of adiposity. In non-smoking women, the coexistence of obesity and low physical activity can explain up to 31% of all premature deaths, 59% of deaths from cardiovascular disease, and 21% of deaths from cancer [25]. Unfortunately, the level of physical activity in the general population is still far from the optimum level. In 2016, the global prevalence of insufficient physical activity was 25.7% and predominated in women and in high-income countries [26]. Among 36 European countries, >30% of the population aged >15 years does less than the minimum level of the recommended physical activity in a typical week. In ten countries, the prevalence of physical inactivity affected >50% of individuals; in 18 countries, the prevalence ranged between 25 and 50%; and in only 9 countries, it was <25% [27].

Table 2
Strength of the evidence of the risk of cancer for obesity, type 2 diabetes and associated risk factors according to the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR).

Cancer site	Obesity	Physical activity	Sedentary behaviour	Red meat	Processed meat	Fish	Dairy products	Alcohol
Oesophageal adenocarcinoma	Sufficient Convincing	– Suggestive			– Suggestive			– Convincing
Gastric cardia	Sufficient Probable							– Probable
Colon and rectum	Sufficient Convincing	– Convincing		– Suggestive	Sufficient Convincing	– Suggestive	– Probable	– Convincing
Liver	Sufficient Convincing	– Suggestive				– Suggestive		– Convincing
Gallbladder	Sufficient Probable							
Pancreas	Sufficient Convincing			– Suggestive	– Suggestive			– Suggestive
Post-menopausal breast	Sufficient Convincing	– Probable						– Convincing
Endometrium	Sufficient Convincing	– Probable	– Suggestive					
Ovary	Sufficient Probable							
Renal adenocarcinoma	Sufficient Convincing							– Probable
Meningioma	Sufficient							
Thyroid	– Sufficient							
Multiple myeloma	– Sufficient							
Male breast	– Limited							
Fatal prostate cancer	– Limited Probable			– Suggestive			– Suggestive	
Diffuse large B-cell lymphoma	Limited							
Oesophageal squamous-cell	–							
Gastric non-cardia					– Suggestive			
Intrahepatic biliary tract								
Lung		– Suggestive		– Suggestive	– Suggestive			– Suggestive
Cutaneous melanoma								– Suggestive
Urinary bladder								
Mouth, pharynx and larynx	– Probable							– Convincing
Cervix	– Suggestive							
Pre-menopausal breast	– Probable	– Suggestive					– Suggestive	– Probable
Nasopharynx				– Suggestive	– Suggestive	– Probable		

Table 2 (*continued.*)

Cancer site	Processed food	Ultra-processed food	Whole grain cereals	Vegetables	Fruits	Type 2 Diabetes	Diabetes and high BMI
Oesophageal adenocarcinoma				– Suggestive			
Gastric cardia							
Colon and rectum			– Probable			(Suggestive)[e]	(Suggestive)[f]
Liver							(Suggestive)[f]
Gallbladder							
Pancreas							
Post-menopausal breast		(Suggestive)[d]		– Suggestive		(Suggestive)[e]	(Suggestive)[f]
Endometrium						(Suggestive)[e]	(Suggestive)[f]
Ovary							
Renal adenocarcinoma							
Meningioma							
Thyroid							
Multiple myeloma							
Male breast							
Fatal prostate cancer							
Diffuse large B-cell lymphoma							
Oesophageal squamous-cell				– Suggestive	– Suggestive		
Gastric non-cardia	– Probable[a]						
Intrahepatic biliary tract						(Suggestive)[e]	
Lung				– Suggestive	– Suggestive		
Cutaneous melanoma							
Urinary bladder				– Suggestive	– Suggestive		
Mouth, pharynx and larynx				– Suggestive			
Cervix							
Pre-menopausal breast							
Nasopharynx	– Suggestive[b,c]			– Suggestive			

Cardiorespiratory fitness is frequently measured by estimating the metabolic equivalents (METs) consumed after a treadmill exercise test. Compared to men with the lowest cardiorespiratory fitness, those with moderate and high cardiorespiratory fitness have a significantly lower risk of developing lung and colon cancers independent of adiposity and smoking status [28]. These results have been reproduced in very long-term studies and meta-analyses. In a prospective study with >40 years of follow-up, men already diagnosed with cancer with high cardiorespiratory fitness had an adjusted 32% lower risk of death related to cancer and a 68% lower risk of death related to cardiovascular causes [29]. With each one MET increase in cardiorespiratory fitness, a 4% reduction in total cancer incidence may be expected [30]. A meta-analyses of six prospective studies also showed a decreased total cancer mortality risk associated with intermediate and high levels of cardiorespiratory fitness, independent of adiposity [31]. The risk of developing breast cancer in pre- or post-menopausal women is also significantly lower among those with the highest cardiorespiratory fitness independent of weight, smoking status, family history of breast cancer, and oral contraceptive or oestrogen use [32].

The WCRF/AICR differentiates recreational, occupational, and total physical activity when estimating risk. They assigned strong and convincing evidence to the association between total and recreational physical activity and the risk of colon cancer. Total, recreational, and occupational physical activity probably decrease the risk of postmenopausal breast cancer. In addition, recreational and occupational physical activities probably decrease the risk of endometrial cancer. They also found limited, although suggestive, evidence that physical activity decreases the risk of lung, liver, and premenopausal breast cancers (Table 2) [13].

A systematic review and meta-analysis of 126 studies in 2016 showed that the WHO recommendations for physical activity decreased cancer risk by 7%, owing to a reduction of breast and colorectal cancer risk [33]. The protective effect on colorectal cancer risk persisted after adjusting for BMI and by family history of colorectal cancer [34].

5.2. Muscular Strength

Adequate muscle mass, strength, and metabolic function are essential to prevent diverse pathologic conditions and chronic diseases [35]. In the clinical setting, muscular strength can be assessed in the upper extremities with a one-repetition maximum supine bench press, and in the lower extremities with a one-repetition maximum seated leg press. Compared to people in the lower tertile of muscular strength, those in the middle and upper tertiles have a significantly lower risk

Table 3
Risk of cancer after intentional weight loss in prospective cohort studies.

Study	Population	Follow-up, years	Subjects who lost weight[a]	Cancer site	Multivariate adjusted HR/RR (95% CI)
Parker, 2003	21,707 post-menopausal women	6	17%	Any	0.89 (0.79–1.00)
				Breast	0.81 (0.66–1.00)
				Colon	0.91 (0.66–1.24)
				Endometrium	0.96 (0.61–1.52)
				Obesity-related[b]	0.86 (0.74–1.01)
Hervy, 2005	33,660 post-menopausal women	15	Lost weight from age 18 to menopause, 2%	Breast	0.36 (0.22–0.60)
			Lost weight from age 30 to menopause and after menopause, 4%		0.48 (0.22–0.65)
			Gained weight until menopause but lost weight after menopause, 8%		0.77 (0.64–0.92)
Eliassen, 2006	49,514 post-menopausal women	26	5%	Invasive breast cancer[c]	0.43 (0.21–0.86)
Rapp, 2007	28,811 men	7	At least 1.30 kg, 17%	Colon[d]	0.50 (0.29–0.97)
Luo, 2017	36,794 post-menopausal women	11.4	7.9%	Endometrium	0.71 (0.54–0.95)
Welti, 2017	80,943 post-menopausal women	20	2.9%	Breast	1.11 (1.03–1.20)
				Endometrium	1.02 (0.62–1.68)
				Colorectum	0.94 (0.65–1.36)

HR, hazard ratio; RR, relative risk; 95% CI, 95% confidence interval.
[a] Unless otherwise specified, most studies considered steady weight loss at least 5 kg or 5% of the basal body weight.
[b] Breast, colon, endometrium, or kidney.
[c] Women who lost weight after menopause and never used hormone replacement therapy.
[d] Weight lost of at least 1.30 kg in 7 years was not associated with a significant reduction in the risk of colon cancer in 36,938 women, and of cancer of the stomach, rectum, prostate, kidney, bladder, and melanoma in men and women.

of cancer mortality regardless of smoking status, BMI, percent of body fat, waist circumference, and cardiorespiratory fitness [36,37].

Thus, performing regular physical activity of at least moderate intensity, avoiding a sedentary lifestyle, and improving physical fitness are of paramount importance to fight against obesity and to decrease the risk of cancer independently of the weight, adiposity, and smoking status [38].

5.3. Sedentary Lifestyle

It is important not only to perform physical activity regularly but also to avoid a sedentary lifestyle the rest of the time, as there is strong evidence that prolonged sedentary time is associated with all-cause mortality and cancer incidence regardless of physical activity level [39,40]. There is a linear association between the time expended on television viewing and the risk of cancer mortality, even after adjusting for physical activity, which becomes significant after expending >4 h per day [41]. Avoiding a sedentary lifestyle is also important for patients already diagnosed with cancer. In cases of cancer of the colon and rectum, leisure physical activity and time expended watching television were both independently associated with mortality [42,43].

The WCRF/AICR considers that, although limited, there is evidence that sedentary behaviour increases the risk of endometrial cancer (Table 3) [44].

6. Nutrition, Food, and Cancer

To ascertain the isolated effects of specific foods from the effects of other nutrients and lifestyle factors is challenging. We now have sufficient evidence of the risk of specific foods regardless of the level of adiposity.

6.1. Red Meat and Processed Meat

Red meat and processed meat deserve special attention due to the extensive investigation in prospective cohort studies, case-control studies, and meta-analyses. Red meat is mammalian muscle meat that is usually consumed cooked. Processed meat is any type of meat, poultry, offal, or meat by-product, such as blood, that is transformed by means of salting, curing, fermenting, smoking, or other processes to enhance flavour or improve preservation. The risk of cancer can be related to the content of fat, the content of residues of veterinary drugs or pollutants, the type of processing meat, and the method of cooking. Based on the positive results of 12 large cohort studies and 9 case-control studies, the IARC Working Group considers that there is sufficient and convincing evidence of a positive association between the consumption of processed meat and the risk of colorectal cancer (Table 2) [45]. In a meta-analysis of 21 studies, red meat and processed meat increased the risk of colorectal cancer approximately linearly. The relative risk was 1.17 (95% CI, 1.05–1.31) for each increase of 100 g/day of red meat and 1.18 (95% CI, 1.10–1.28) for each increase of 50 g/day of processed meat [46]. There is also an association, though considered weak, between consumption of processed meat and cancer of the stomach, and of red meat and cancer of the colorectum, pancreas, and prostate. The overall evaluation of the IARC, assumed by the WHO, is that the consumption of processed meat is carcinogenic to humans, and consequently, it has been classified, together with tobacco, as a Group 1 carcinogen. Consumption of red meat is considered to be probably carcinogenic to humans (Group 2A) [45].

The WCRF/AICR found the risk of colorectal cancer associated with the consumption of >50 g/day of processed meat convincing. The level of evidence was limited and suggestive for cancers of the nasopharynx, oesophagus (squamous cell), lung, stomach (non-cardia), and pancreas. Consumption of >100 g/day of red meat probably increases the risk of cancer of the colorectum. The evidence is limited but suggestive for cancers of the nasopharynx, lung, and pancreas (Table 2) [13].

The consumption of processed meat has also been associated with cancer mortality in a meta-analysis of 17 cohort studies with a pooled RR of 1.08 (95% CI, 1.06–1.11) [47].

6.2. Fish

There is extensive literature about the potential effect of fish consumption on cancer risk but with variable results. The WCRF/AICR considers that there is limited but suggestive evidence of a protective effect of the consumption of 20 g/day of fish for liver cancer (RR 0.94; 95% CI, 0.89–0.99), and of 100 g/day for colorectal cancer (RR 0.89; 95% CI, 0.80–0.99). In contrast, the consumption of salted fish, including Cantonese-style salted fish, was considered to increase the risk of nasopharynx cancer (Table 2).

Dietary supplementation with fish oils has recently gained acceptance to improve cardiovascular health and even to prevent cancer. In vitro cell studies and animal models, n−3 polyunsaturated fatty acids

(n−3 PUFA) have been demonstrated to inhibit carcinogenesis. However, the results of observational studies in humans are discordant for different cancer types and for the same type of cancer. A meta-analysis in 2013 of 26 publications including 883,585 women concluded that the consumption of at least 0.1 g/day of n−3 PUFA was associated with a 14% reduction in the risk of breast cancer [48]. Another meta-analysis of 14 prospective studies found no relationship between n−3 PUFA consumption and risk of colorectal cancer [49]. In the case of prostate cancer, a meta-analyses of 16 publications found that certain types of n−3 PUFAs, such as docosahexaenoic acid, were associated with an increased risk of cancer, whereas alpha-linolenic acid was inversely associated with the risk of prostate cancer. In addition, blood eicosapentaenoic acid and docosahexaenoic acid concentrations were also associated with aggressive prostate cancer [50].

6.3. Dairy Products and Eggs

The risk has been assessed separately for milk, cheese, dietary calcium, and overall dairy products in prospective studies and meta-analyses. Increments of 200 g/day of milk, 50 g/day of cheese, 200 mg/day of dietary calcium, and 400 g/day of dairy products have been found by the WCRF/AICR to decrease the risk of colorectum and breast (pre-menopause) cancer with a level of evidence probable and suggestive, respectively [13]. A meta-analyses of 11 cohort studies with 778,929 individuals concluded that the consumption of whole milk increases the risk of prostate cancer (pooled RR 1.50; 95% CI, 1.03–2.17). The WCRF/AICR concluded that the relationship between consumption of >400 g/day of dairy products and the risk of prostate cancer is suggestive [13,51].

In a meta-analyses of 2014, an association between the consumption of eggs and the risk of breast cancer was observed in cohort studies for people who consumed 2 to 5 eggs per week, but not in case-control studies, nor in people who consumed >5 eggs per week [52]. In a meta-analysis of 12 studies with 629,453 participants, those with the maximum consumption of eggs had a significantly increased risk of ovarian cancer. This effect was only observed in women who participated in case-control studies but not in cohort studies [53]. The disparity of these results suggests that chance, bias, and confounding factors may not be ruled out with confidence.

6.4. Alcohol

Alcohol consumption has become the third leading preventable cause of death in the US after tobacco and physical inactivity and inadequate nutrition [54]. In 2016, 5.3% of all global deaths were attributable to alcohol consumption [55]. Alcohol also significantly contributes to weight gain and to the risk of overweight and obesity-related cancers. It should be taken into account that 1 g of alcohol contributes 7 kcal, whereas 1 g of carbohydrate or protein contributes only 4 kcal. The content in grams of ethanol in alcoholic beverages can be estimated by multiplying the percentage of alcohol by the total volume and by 0.008. Thus, the ethanol content of 330 ml of a 5% volume alcoholic beer contributes 92.4 kcal, 100 ml of red wine contributes 67 kcal, and 100 ml of whisky or gin contributes 224 kcal.

A meta-analyses of 572 studies published through 2012 provided a quantitative estimation of the strength of the association between alcohol consumption and the risk of cancer, and a categorization of alcohol consumption as light (≤12.5 g/day of alcohol), moderate (between 12.5 and 50 g/day), and heavy (≥50 g/day) [56]. Compared with non-drinkers or light drinkers, heavy drinkers showed an increased relative risk of oral and pharyngeal cancer (RR 5.13; 95% CI, 4.31–6.10), oesophageal squamous-cell carcinoma (RR 4.95; 95% CI, 3.86–6.34), colorectal carcinoma (RR 1.44; 95% CI, 1.25–1.68), laryngeal carcinoma (RR 2.65; 95% CI, 2.19–3.19), and female breast cancer (RR 1.61; 95% CI, 1.33–1.94). There was a clear dose-risk relationship between alcohol consumption and the risk of these five types of cancer. Heavy drinkers also had a significantly increased risk, without clear dose-risk relationships, of cancer of the stomach, liver, gallbladder, pancreas, and lung. Conversely, heavy alcohol consumption exerted a protective effect on the risk of Hodgkin's lymphoma (RR 0.63, 95% CI, 0.41–0.97), and non-Hodgkin's lymphoma (RR 0.75; 95% CI, 0.64–0.88) [56].

The WCRF/AICR has found strong and convincing evidence of the relationship between alcohol consumption and the risk of the cancer of mouth, pharynx, and larynx, oesophagus (squamous cell), liver, colorectum, breast (post-menopause). The level of evidence was considered strong but probable in cases of cancer of stomach and breast (premenopause) and limited but suggestive in cancers of the lung, pancreas, and skin (basal cell carcinoma and melanoma). They also found a protective effect of alcohol consumption for kidney cancer (Table 2) [13].

6.5. Ultra-processed Food

Foods can be classified according to the extent and purposing of food processing, which can be associated with unhealthy nutrient profiles and diet-related non-communicable diseases. Reports from the Food and Agriculture Organization of the United Nations and the Pan American Health Organization have recognized and used the NOVA system that categorizes all foods into 4 groups according the extent of processing [57]. Group 1 is composed of unprocessed or minimally processed foods; Group 2 is processed culinary ingredients that are obtained directly from Group 1 foods, such as sugar, salt, honey, vegetable oils, butter, and starches; Group 3 is processed foods made by adding two or three ingredients, such as sugar, oil, salt or other Group 2 substances to Group 1 foods, or processed foods by various preservation methods, or non-alcoholic fermentation (cheese); and Group 4 is composed of ultra-processed foods and drink products, which are industrial formulations usually with five or more ingredients, including antioxidants, stabilizers, and preservatives.

The NutriNet-Santé was a French population-based cohort study launched in 2009 to assess dietary behaviours and nutritional determinants of health. A total of 104,980 participants were categorized into four groups according to the proportion of ultra-processed food in the total diet. Compared to the first quarter of participants that consumed less ultra-processed food, the fourth quarter was associated with a significant increased overall cancer risk (RR 1.23; 95% CI, 1.08–1.40) and risk of post-menopausal breast cancer (RR 1.38; 95% CI, 1.05–1.81) after adjusting for energy intake, smoking status, physical activity, BMI, alcohol intake, menopausal status, hormonal treatment, oral contraception, and Western dietary pattern. They estimated a 10% increased risk of overall and breast cancer for a 10% increase in the proportion of ultra-processed food. There was also a borderline but non-significant increased risk of colorectal cancer (RR 1.23; 95% CI, 1.08–1.40; $p = 0.07$). The food groups that most frequently contributed to ultra-processed food composition were sugary products (26%), drinks (20%), starchy foods and breakfast cereals (16%), and ultra-processed fruits and vegetables. This study could not address the relative contribution of the processing methods, nutritional composition, food additives, contact materials, and neoformed contaminants (Table 2) [58].

6.6. Whole Grain Cereals and Nuts

There is extensive concordance in the protective effects of whole grain cereals from cancer mortality in different meta-analyses. Consumption of each 90 g/day of total whole grains is associated with a reduction of 9% in cancer mortality [59–61]. The conclusions of the WCRF/AICR are that each 90 g/day increment of whole grains decreases the risk of cancer of the colorectum with a level of evidence probable (Table 2) [13].

High versus low consumption of tree nuts and peanuts are also associated with a decreased risk of cancer mortality. In a dose-response

analysis, each 10 g/day increment in the intake of tree nuts reduced the RR by 0.80 (95% CI, 0.72–0.89) [62]. High consumption of nuts has been related to a decreased risk of cancer of the post-menopausal breast (negative oestrogen receptor), endometrium, pancreas, and gastrointestinal tract [63–65]. In a case-control study, consumption of three or more servings per week of nuts was strongly associated with a reduction of cancer of the distal colon and rectum in men and women and of the proximal colon in men. The association remained significant after adjusting for age, alcohol consumption, physical activity, BMI, consumption of red meat, fruits and vegetables, and total energy intake [66].

6.7. Fruits and Vegetables

Regular consumption of fruits and vegetables was protective against cancer mortality in a meta-analysis of prospective studies, with a reduction in the RR of 3–4% for each 200 g/day increment of intake [67]. The WCRF/AICR judgement is that there is limited evidence about the protective effect of fruits and non-starchy vegetables on specific cancers of different localizations (Table 2) [13].

6.8. Eating Patterns and High-quality Diets

Recommendations about food and nutrition directed to decrease the risk of cancer, diabetes, cardiovascular disease, and mortality should not be based on the promotion or discouragement of particular foods. It should be based on the promotion of healthy eating patterns and high-quality diets that include all the updated best evidence-based knowledge. Thus, current dietary recommendations of the WCRF/AICR, the American Cancer Society, and the IARC European Code against Cancer Secretariat are directed towards limiting the consumption of energy dense foods, sugar-sweetened beverages, refined carbohydrates, salt, alcohol, animal-based foods, and particularly, processed meat. They promote the consumption of whole grain cereals, nuts, legumes, fruits and vegetables and, in general, plant-based foods. For those who choose to include animal-based foods, it is preferable to choose fish and poultry as an alternative to red meat. For those who want to eat red meat, it is recommended to select lean cuts and eat small portions [13,68,69]. The protective effect against cancer risk of these recommendations has been evaluated with favourable results using different eating scores, such as the Healthy Eating Index, the Alternative Healthy Eating Index, the Dietary Approaches to Stop Hypertension, and the Mediterranean pattern diet [70–73].

7. Mechanisms of Oncogenic Transformation in Obesity and Type 2 Diabetes

The complex biologic changes that follow adipose tissue expansion and pre-dispose to oncogenic transformation are not fully understood. The expanded adipose tissue is responsible for an unbalanced production of adipokines. It is also associated with elevated levels of oestrogens driven by an increase in aromatase activity within adipocytes and by decreased levels of sex hormone-binding globulins. In obesity, and

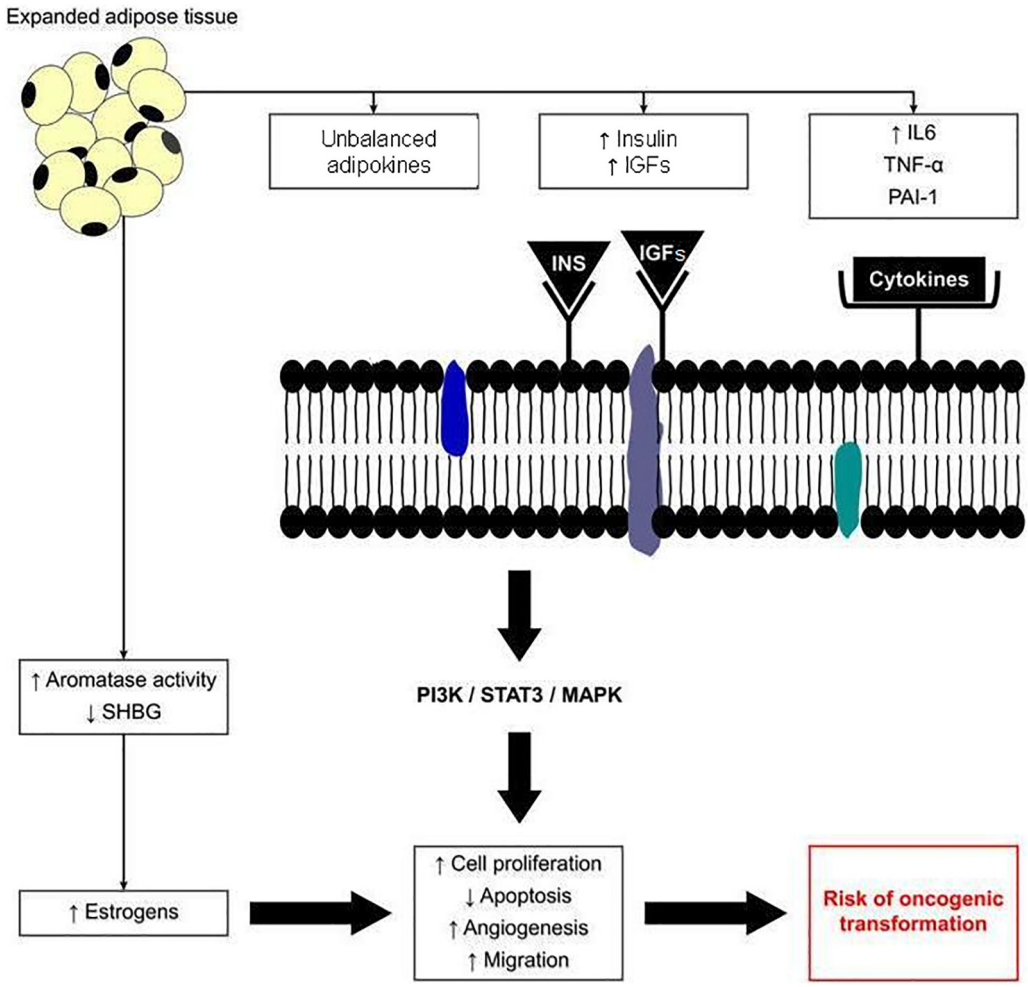

Fig. 2. Signalling pathways and risk of cancer of expanded adipose tissue. IGFs, insulin growth factors; IL6, interleukin 6; MAPK, mitogen-activated protein kinase; PAI-1, plasminogen activator inhibitor 1; PI3K, phosphatidylinositol 3-kinase; SHBG, sex hormone-binding globulin; STAT3, signal transducer and activator of transcription 3; TNF-α, tumour necrosis factor-α.

particularly in type 2 diabetes, there is a state of upregulation in the receptors of insulin growth factors (IGFs), hyperinsulinaemia, insulin resistance, and dyslipidaemia. Obesity and type 2 diabetes are also associated with changes in non-adipose cells in the stromal-vascular component of the adipose tissue that are responsible for an inflammatory state by stimulating macrophages and other inflammatory cells to increase the levels of interleukin 6, tumour necrosis factor-α, and plasminogen activator inhibitor 1. Unbalanced adipokines, insulin, IGFs, and pro-inflammatory cytokines activate cell membrane receptors that drive complex changes in several signalling pathways, mainly that of phosphatidylinositol 3-kinase, signal transducer and activator of transcription 3, and mitogen-activated protein kinase. All of these changes are believed to play a critical role in the risk of oncogenic transformation by favouring cell proliferation and migration, angiogenesis, and reducing cell apoptosis (Fig. 2) [74–76].

8. Effects of Intentional Weight Loss and Type 2 Diabetes Therapies on Cancer Incidence

The strength of evidence about the effects of intentional weight loss on the risk of cancer is weak and limited. The number of well-designed, large, prospective studies is very scarce. There is no accordance about the magnitude of the weight reduction and the period of time in which it should be attained or must be maintained. However, the most critical limitation may be the very limited proportion of obese people who achieve a durable weight loss of at least 5 kg or 5% of the basal body weight. In most studies, this figure is usually <5–10%. From the available information from cohort studies, there seems to be suggestive evidence of a reduction in the risk of breast cancer in post-menopausal women who attain weight loss that is maintained without significant fluctuations over time (Table 3) [77–82].

Compared with the standard treatment of obesity based on changes in diet and physical activity, bariatric surgery has the advantage of achieving dramatic and sustained weight loss of up to 20 kg over 10 years [83]. In a systematic review and meta-analyses of six observational studies with 51,740 participants, compared with obese controls, the relative risk of cancer in obese patients subjected to bariatric surgery was 0.50 (95% CI, 0.41–0.73). After stratifying by sex, the benefits were demonstrated only in women [84].

Therapeutic choices of type 2 diabetes may have implications for the risk of cancer. Some data suggest that insulin and oral secretagogues may increase the risk of cancer compared to patients taking metformin or thiazolidinediones. However, these data are retrospective and may be affected by confounding factors because patients taking insulin typically have more advanced and long-lasting disease. Whether metformin or thiazolidinediones confer protective effects beyond model systems also remains unclear [74]. Glucagon-like peptide-1 (GLP-1) analogues are incretin-based antidiabetic drugs that have the advantage of inducing significant and prolonged weight loss in obese patients with type 2 diabetes, and thus, they could be beneficial to reduce the risk of cancer. However, some data have raised concerns about a higher risk of some types of cancer after 2–3 years of treatment. To date, there is neither firm evidence in favour of GLP-1-based therapy increasing the risk of specific cancers, nor evidence to rule out any such increased risk. Until more information becomes available, this controversy should not be taken into account when making treatment decisions [85,86].

9. Healthy Lifestyle: One Size Fits All Approaches for Obesity, Cancer, CVD, and Mortality

The cornerstone of prevention relies on promoting a healthy lifestyle favouring healthy foods and physical activity and reducing overeating, excessive alcohol intake, and tobacco smoking. These measures have a favourable impact on cancer and CVD incidence, both indirectly through their benefits on reducing overweight and directly regardless of the magnitude of overweight.

The impact of a healthy lifestyle on human health is impressive. Using data from the European Prospective Investigation into Cancer and Nutrition Cohort, it has been quantified the joint effect of five modifiable risk factors (healthy diet pattern, physical activity, smoking, alcohol intake, and BMI) on the risk of total cancers and cancers related to alcohol, tobacco, and obesity. For a score from 0 (the worst lifestyle) to 10 (the best lifestyle), there was a 5% lower risk in men and 4% lower risk in women for all cancers for each score point. Compared with the worst scoring category, the best scoring category was associated with a 28% lower risk across all cancers in men and 24% lower risk in women [87].

A recent analyses with the data from the Nurses´ Health Study, the Health Professional Follow-up Study, and the NHANES 2013–2014 has provided incontestable results [88]. They investigated the effects on all-cause and specific-cause mortality of a lifestyle score constructed with smoking, BMI, alcohol intake, physical activity, and a high diet quality score (upper 40%). The population-attributable risk of non-adherence to the five risk factors was 60.7% for all-cause mortality, 51.7% for cancer mortality, and 71.7% for CVD mortality. In women and men at the optimum level of the five risk factors, the projected life expectancy at age 50 years was 14.0 and 12.2 years longer, respectively, compared with those at the worst level.

In conclusion, approximately 30 to 40% of the most common cancers are preventable by avoiding smoking and preventing overweight by adopting a healthy lifestyle. Having a healthy lifestyle means engaging in regular physical activity; choosing a predominantly plant-based diet that limits the consumption of red meat, alcohol, and ultra-processed foods, particularly of red processed meat; and selecting legumes, nuts, dry fruits, and fish as the main source of proteins. Education to promote positive choices has to be continuously reinforced throughout all periods of life. However, public health interventions on food delivery are also requested to reduce the burden of obesity-related cancers and lighten the unsustainable growing expenses to health systems.

Conflict of Interests

I do not have any conflict of interest to disclose.

Acknowledgements

Thanks to the Fundación Doctor Pascual and to Hospitales Docentes José Manuel Pascual for their support.

References

[1] International Agency for Cancer on Research. http://publications.iarc.fr/Book-And-Report-Series/Iarc-Working-Group-Reports/Energy-Balance-And-Obesity-2017, Accessed date: 14 August 2018.
[2] OECD. Obesity update 2017; 2017 [Accessed August 13, 2018].
[3] Calle EE, Rodríguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348:1625–38.
[4] Ligibel JA, Alfano CM, Demark-Wahnefried W, Burger RA, Chlebowski RT, Fabian CJ, et al. American Society of Clinical Oncology position statement on obesity and cancer. 2014;32:3568–74.
[5] Annual medical spending attributable to obesity: payer-and service-specific estimates, Health Aff (Millwood) 2009;28:822–8331.
[6] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analyses for the Global Burden of Disease Study 2013. Lancet 2014;384:766–81.
[7] Marques A, Peralta M, Naia A, Loureiro N, de Matos MG. Prevalence of adult overweight and obesity in 20 European countries, 2014. Eur J Public Health 2018;28: 295–300.
[8] Brooke Steele C, Thomas CC, Henley SJ, Massetti GM, Gauska DA, Agurs-Collins, et al. Vital signs: trends in incidence of cancers associated with overweight and obesity - United States, 2005–2014. MMWR 2017;66:1052–8.
[9] Prospective Studies CollaborationWhitlock G, Lewington S, Sherliker P, Clark R, Emberson J, et al. Body-mass index and cause-specific mortality in 900000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083–96.

[10] Keum N, Greewood DC, Lee DH, Kim R, Aune D, Hu FB, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst 2015;107. https://doi.org/10.1093/jnci/djv088.
[11] Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchi F, et al. Body fatness and cancer - viewpoint of the IARC Working Group. N Engl J Med 2016;375:794–8.
[12] Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 2015;16:36–46.
[13] World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project expert report 2018. Available at http://dietandcancerreport.org.
[14] International Agency for Research on Cancer. http://www.iarc.fr/en/media-centre/iarcnews/2016/handbook16_iarc2016.php; 2018.
[15] Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017;356. https://doi.org/10.1136/bmj.j477.
[16] International Diabetes Federation AtlasEight ed. ; 2017 Available from http://www.diabetesatlas.org, Accessed date: 22 August 2018.
[17] Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102–7.
[18] Thompson AM, Church TS, Janssen I, Katzmarzyk, Earnest CP, Blair SN. Cardiorespiratory fitness as a predictor of cancer mortality among men with prediabetes and diabetes. Diabetes Care 2008;31:764–9.
[19] Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EN, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analysis of observational studies. BMJ 2015;350:g7607. https://doi.org/10.1136/bmj.g7607.
[20] Chen Y, Wu F, Saito E, Lin Y, Song M, Luu HN, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771000 individuals in the Asia Cohort Consortium. Diabetologia 2017;60:1022–32.
[21] Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter M, Ezzati M. Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol 2018;6:e6-15.
[22] Arem H, Moore SC, Patel A, Hartge P, Berrington A, Phil D, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med 2015;175:959–67.
[23] O'Donovan G, Lee IM, Hamer M, Stamatakis E. Association of "weekend warrior" and other leisure time physical activity patterns with risks for all-cause, cardiovascular disease, and cancer mortality. JAMA Intern Med 2017;177:335–42.
[24] Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med 2016;176:816–25.
[25] Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity compared with physical activity in predicting mortality among women. N Engl J Med 2004;351:2694–703.
[26] Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Glob Health 2018;6:e1077–86.
[27] World Health Organisation. http://www.euro.who.int/__data/assets/pdf_file/0004/243337/Summary-document-53-MS-country-profile.pdf?ua=1, Accessed date: 14 August 2018.
[28] Jensen MT, Holtermann A, Bay H, Gyntelberg F. Cardiorespiratory fitness and death from cancer: a 42-year follow-up from Copenhagen Male Study. Br J Sports Med 2017;51:1364–9.
[29] Lakoski SG, Willis BL, Barlow CE, Leonard D, Gao A, Radford NB, et al. Midlife cardiorespiratory fitness, incident cancer, and survival after cancer in men. The Cooper Center Longitudinal Study. JAMA Oncol 2015;1:231–7.
[30] Vainshelboim B, Müller J, Lima RM, Nead KT, Chester C, Chan K, et al. Cardiorespiratory fitness and cancer incidence in men. Ann Epidemiol 2017;27:442–7.
[31] Schmid D, Leitzmann. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol 2015;26:272–8.
[32] Peel JB, Sui X, Adams SA, Hébert JR, Hardin JW, Blair SN. A prospective study of cardiorespiratory fitness and breast cancer mortality. Med Sci Sports Exerc 2009;41:742–8.
[33] Liu L, Shi Y, Li T, Qin Q, Yin J, Pang S, et al. Leisure time physical activity and cancer risk: evaluation of the WHO's recommendation based on 126 high-quality epidemiological studies. Br J Sports Med 2016;50:372–8.
[34] Shaw E, Farris MS, Stone CR, Derksen JWG, Johnson R, Hilsden RJ, et al. Effects of physical activity on colorectal cancer risk among family history and body mass index subgroups: a systematic review and meta-analysis. BMC Cancer 2018. https://doi.org/10.1186/s12885-017-3970-5.
[35] Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr 2006;84:475–82.
[36] Ruiz JR, Sui X, Lobelo F, Lee D, Morrow JR, Jackson AW, et al. Association between muscular strength and mortality in men: prospective cohort study. BMJ 2008;337:92–5.
[37] Ruiz JR, Sui X, Lobelo F, Lee D, Morrow JR, Jackson AW, et al. Muscular strength and adiposity as predictors of adulthood cancer mortality in men. Cancer Epidemiol Biomarkers Prev 2009;18:1468–75.
[38] Ekelund U, Steene-Johannsessen J, Fagerland MW, Owen N, Powell KE, Bauman AE, et al. Do the association of sedentary behavior with cardiovascular disease mortality and cancer mortality differ by physical activity level? A systematic review and harmonized meta-analysis of data from 850060 participants. Br J Sports Med 2018. https://doi.org/10.1136/bjsports-2017-098963.
[39] Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015;162:123–32.
[40] Ekelund U, Steene-Johannsessen J, Brown WJ, Fagerlan MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonized meta-analysis of data from more than 1 million men and women. Lancet 2016;388:1302–10.
[41] Patterson R, McNamara E, Tainio M, Hérick de Sá T, Smith AD, Sharp SJ, et al. Sedentary behavior and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol 2018. https://doi.org/10.1007/s10654-018-0380-1.
[42] Arem H, Pfeiffer RM, Engels EA, Alfano CM, Hollenbeck A, Park Y, et al. Pre- and postdiagnosis physical activity, television viewing and mortality among patients with colorectal cancer in the National Institutes of Health-AARP Diet and Health Study. J Clin Oncol 2015;33:180–8.
[43] Ratjen I, Schafmayer C, di Guiseppe R, Waniek S, Plachta-Danielzik S, Koch M, et al. Postdiagnosis physical activity, sleep duration, and TV watching and all-cause mortality among long-term colorectal cancer survivors: a prospective cohort study. BMC Cancer 2017;17:701. https://doi.org/10.1186/s12885-017-3697-3.
[44] World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project report 2018. Physical activity and the risk of cancer. Available at http://dietandcancerreport.org.
[45] Red meat and processed meat. IARC Monographs on the evaluation of carcinogenic risks to human 2018;114https://www.ncbi.nlm.nih.gov/books/NBK507971/, Accessed date: 14 August 2018.
[46] Chan DSM, Lau R, Aune D, Vieira R, Greenwood DC, Jampman E, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011;6:e2046. https://doi.org/10.1371/journal.pone.0020456.
[47] Wang X, Lin X, Ouyang YY, Liu J, Zhao G, Pan A, et al. Red and processed meat consumption and mortality: dose-response meta-analysis of prospective cohort studies. Public Health Nutr 2016;19:893–905.
[48] Zheng JS, Hu XJX, Zhao YM, Yang J, Li D. Intake of fish and marine n−3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ 2013;346:f3706. https://doi.org/10.1136/bmj.f3706.
[49] Chen GC, Qin LQ, Han TM, Zheng Y, Xu GZ, Wang XH. N−3 polyunsaturated fatty acids intake and risk of colorectal cancer: meta-analysis of prospective studies. Cancer Causes Control 2015;26:133–41.
[50] Fu YQ, Zheng JS, Yamg B, Li D. Effect of individual omega-3 fatty acids on the risk of prostate cancer: a systematic review and dose-response meta-analysis of prospective cohort studies. J Epidemiol 2015;25:261–74.
[51] Lu W, Chen H, Niu Y, Wu H, Xia D, Wu Y. Dairy products intake and cancer mortality risk: a meta-analysis of 11 population-based cohort studies. Nutr J 2016;1. https://doi.org/10.1186/s12937-016-0210-9.
[52] Si R, Qu K, Jiang Z, Yang X, Gao P. Egg consumption and breast cancer risk: a meta-analysis. Breast Cancer 2014;21:251–61.
[53] Zeng ST, Guo L, Liu SK, Wang SK, Xi J, Huang P, et al. Egg consumption is associated with increased risk of ovarian cancer: evidence from a meta-analysis of observational studies. Clin Nutr 2015:34635–41.
[54] Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States 2000. JAMA 2004;291:1238–45.
[55] World Health Organization (WHO). Global Status Report on Alcohol and Health. http://www.who.int/substance_abuse/publications/global_alcohol_report/gsr_2018/en/, Accessed date: 4 October 2018.
[56] Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015;112:580–3.
[57] Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MCL, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr 2018;21:5–17.
[58] Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ 2018;360:k322. https://doi.org/10.1136/bmj.k322.
[59] Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greewood DC, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. BMJ 2016;353. https://doi.org/10.1136/bmj.i2716.
[60] Zong G, Gao A, Hu FB, Sun Q. Whole grain intake and mortality from all causes, cardiovascular disease, and cancer. A meta-analysis of prospective cohort studies. Circulation 2016;133:2370–80.
[61] Wei H, Gao Z, Liang R, Li Z, Hao H, Liu X. Whole-grain consumption and the risk of all-cause, CVD and cancer mortality: a meta-analysis of prospective cohort studies. Br J Nutr 2016;116:514–25.
[62] Aune D, Keum N, Fadnes LT, Bofferra P, Greenwood DC, Tonstad S, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med 2016. https://doi.org/10.1186/s12916-016-0730-3.
[63] Van en Brandt PA, Nieuwenhuis L. Tree nut, peanut, and peanut butter intake and the risk of postmenopausal breast cancer. The Netherlands Cohort Study. Cancer Causes Control 2018;29:63–75.
[64] Wu L, Wang Z, Zhu J, Murad AL, Prokp LJ, Murad MH. Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis. Nutr Rev 2015;73:409–25.
[65] Eslamparast T, Sharafkhah M, Poustchi H, Hashemian M, Dawsey SM, Freedman ND, et al. Nut consumption and total and cause-specific mortality: results from the Golestan Cohort Study. Int J Epidemiol 2017;46:75–85.
[66] Lee J, Shin A, Oh JH, Kim J. The relationship between nut intake and risk of colorectal cancer: a case control study. Nutr J 2018;17:37. https://doi.org/10.1186/s12937-018-0345-y.

[67] Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all cause mortality - a systematic review and dose response meta-analysis of prospective studies. Int J Epidemiol 2017;46:1029–56.
[68] Kushi LH, Doyle C, McCullough M, Rock CR, Demark-Wahnefried W, Bandera EV, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention. Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2012;62:30–67.
[69] Nrat T, Scoccianti C, Boutron-Ruault MC, Anderson A, Berrino F, Cecchini M, et al. European Code Against cancer 4th Edition: diet and cancer. Cancer Epidemiol 2015;39(Suppl. 1):S56–66.
[70] Jankovic N, Geelrn A, Winkels RM, Mwungura B, Fedirko V, Jenab M, et al. Adherence to the WCRF/AICR dietary recommendations for cancer prevention and risk of cancer in elderly from Europe and United States: a meta-analysis within the CHANCES Project. Cancer Epidemiol Biomarkers Prev 2017;26:136–44.
[71] Onvani S, Haghighatdoost F, Surkan PJ, Larijani B, Azadbakht L. Healthy Eating Index dietary patterns and mortality from all causes, cardiovascular disease and cancer: a meta-analysis of observational studies. J Hum Nutr Diet 2017;30:216–26.
[72] Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A. Association of changes in diet quality and cause-specific mortality. N Engl J Med 2017;377:143–53.
[73] Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis. Nutrients 2017;9. https://doi.org/10.3390/nu9101063.
[74] Khandekar M, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 2011;11:886–95.
[75] Hopkins BD, Goncalves MD, Cantley LC. Obesity and cancer mechanisms: cancer metabolism. J Clin Oncol 2016;34:4277–83.
[76] Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: a review of current evidence. Endocr Rev 2012;33:547–94.
[77] Parjer ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Healthy Study. Int J Obes Relat Metab Disord 2003;27:1447–52.
[78] Harvie M, Howell A, Vierkant RA, Kumar N, Cerhan JR, Kelemen LE, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2005;14:656–61.
[79] Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA 2006;296:193–201.
[80] Rapp K, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, et al. Weight change and cancer risk in a cohort of more than 65000 adults in Austria. Ann Oncol 2008;19:641–8.
[81] Luo J, Chlebowski RT, Hendryx M, Rohan T, Wactawski-Wende J, Thomson CA, et al. Intentional weight loss and endometrial cancer risk. J Clin Oncol 2017;35:1189–93.
[82] Welti LM, Beavers DP, Caan BJ, Sangi-Haghpeykar H, Vitolins MZ, Beavers KM. Weight fluctuation and cancer risk in post-menopausal women: the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev 2017;26:779–86.
[83] Sjöström L, Gummesson A, Sjöström CD, Narbro K, Peltonem M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study). A prospective, controlled intervention trial. Lancet Oncol 2009;10:653–62.
[84] Tee MC, Cao Y, Warnock GL, Hu FB, Chavarro JE. Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis. Surg Endosc 2013;27:4449–56.
[85] Nauck MA, Friedrich N. Do GLP-1-based therapies increase cancer risk? Diabetes Care 2013;36(Suppl. 2):s245–52.
[86] Hicks BM, Yin H, Yu OHY, Pollak MN, Platt RW, Azoulay L. Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study sing the UK Clinical Practice Research Datalink. BMJ 2016;355. https://doi.org/10.1136/bmj.i5340.
[87] McKenzie F, Biessy C, Ferrari P, Freisling H, Rinaldi S, Chajès V, et al. Healthy lifestyle and risk of cancer in the European Prospective Investigation into Cancer and Nutrition Cohort Study. Medicine (Baltimore) 2016;95:e2850. https://doi.org/10.1097/MD.0000000000002850.
[88] Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, et al. Impact of healthy lifestyle factors on life expectancies in the US population. Circulation 2018;138:345–55.