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Mediterranean diet and olive oil, microbiota, and obesity-related cancers. From mechanisms to prevention

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ABSTRACT

Olive oil (OO) is the main source of added fat in the Mediterranean diet (MD). It is a mix of bioactive compounds, including monounsaturated fatty acids, phytosterols, simple phenols, secoiridoids, flavonoids, and terpenoids. There is a growing body of evidence that MD and OO improve obesity-related factors. In addition, obesity has been associated with an increased risk for several cancers: endometrial, oesophageal adenocarcinoma, renal, pancreatic, hepatocellular, gastric cardia, meningioma, multiple myeloma, colorectal, postmenopausal breast, ovarian, gallbladder, and thyroid cancer. However, the epidemiological evidence linking MD and OO with these obesity-related cancers, and their potential mechanisms of action, especially those involving the gut microbiota, are not clearly described or understood. The goals of this review are 1) to update the current epidemiological knowledge on the associations between MD and OO consumption and obesity-related cancers, 2) to identify the gut microbiota mechanisms involved in obesity-related cancers, and 3) to report the effects of MD and OO on these mechanisms.

1. Introduction

The Mediterranean diet (MD) is primarily a plant-based dietary pattern, consisting of a high intake of fruit, vegetables, legumes, nuts and seeds, whole grains, spices, herbs, and olive oil (OO). Seafood, poultry, eggs, wine (during meals), and dairy products preferably in the form of low-fat cheese and yoghurt are consumed in moderation, while red and processed meats, refined grains and sugars are little or occasionally consumed [1]. Owing to its food composition, the MD is a dietary pattern rich in protective nutrients and bioactive compounds able to prevent several diseases, including obesity and cancer [2].

OO is the main source of fat in the MD [3–6]. OO's chemical composition differs according to olive variety, environmental conditions, ripening, and processing methods. OO has both a saponifiable fraction and a phenolic one. Oleic acid is the main component of the saponifiable fraction; phenolic acids, tyrosols, flavonoids, and lignans are the main components of the phenolic part of virgin olive oil (VOO) [7–9]. Depending on the processing methods, OOs can be classified into

Abbreviations: AICR, American Institute of Cancer Research; BMI, Body mass index; CRC, Colorectal cancer; EFSA, European Food Safety Authority; EPIC, European Prospective Investigation into Cancer and Nutrition; EVOO, Extra virgin olive oil; GERD, Gastroesophageal reflux disease; GM, Gut microbiota; HR, Hazard Ratio; HT, Hydroxytyrosol; IARC, International Agency for Research on Cancer; IGF-I, Insulin-like growth factor-I; IL, Interleukin; LPS, Lipopolysaccharides; MAMP, Microorganism-associated molecular patterns; MD, Mediterranean Diet; OO, Olive oil; PC, Phenolic compounds; PREDIMED, Prevention with Mediterranean Diet; RR, Relative Risk; SCFA, Short chain fatty acid; SHBG, Sex hormone-binding globulin; TMAO, Trimethylamine-N-oxide; TNF-α, Tumour necrosis factor-alpha; VOO, Virgin olive oil; WCRF, World Cancer Research Fund.

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refined OO, common OO, VOO, or extra virgin OO (EVOO). EVOO and VOO are obtained by direct pressing or centrifugation of the olives and are rich in phenolic compounds (PC). Hydroxytyrosol (HT), a phenol, is the main component responsible for VOO's antioxidant effect on low-density lipoproteins, as endorsed by a European Food Safety Authority (EFSA) health claim in 2011. The Fatty acid composition and its richness in antioxidants are responsible for VOO's stability upon heating and may counteract the generation of oxidation-derived pro-carcinogenic molecules such as polycyclic aromatic hydrocarbons and heterocyclic amines [10]. As a result, VOO exhibits high resistance against oxidation in comparison with other oils, and during its use for frying, when the oil is frequently reloaded, its chemical composition is less altered.

The relationship between MD and obesity and obesity-related disorders has been extensively investigated over the past two decades [11]. MD is an effective tool in reducing body weight, particularly when energy is restricted and in combination with increased physical activity [12,13]. Reassuringly, even when MD is not energy-restricted, it is not associated with adulthood weight gain in the short or long term [14]. In addition, a growing body of evidence suggests that higher adherence to MD is related to a lower risk of cancer mortality in the general population, and cancer-specific and all-cause mortality among cancer survivors [15,16].

One of the contributing factors of obesity is gut microbiome dysbiosis. Then, microbiota modulation through diet could play a relevant role in obesity and obesity-related cancer prevention and treatment. The holobiont and the symbiotic relationship between microbiota and host must be seriously considered when studying human metabolism and obesity. Concretely, the holobiont is defined as an assemblage of a host and the other species living in or around it, which collectively form a discrete ecological unit [17]. The holobiont includes the host, virome, microbiome, and any other organisms which contribute to functioning as a whole [18]; this concept was initially introduced by Adolf Meyer-Abich and refined by Dr. Lynn Margulis in the early nineties [17].

In this review, we provide an overview of the epidemiological evidence on the associations between obesity and cancer, and between MD and OO and obesity-related cancers. In addition, we describe the microbiota mechanisms involved in the link between obesity and cancer and highlight how MD and olive oil can modulate gut microbiota (GM). The elucidation of these relationships could be relevant for the development of preventive, diagnostic, and therapeutic strategies against obesity-related cancers.

2. Obesity and cancer risk: epidemiological evidence

Obesity is a complex multifactorial disease defined as an excessive body fat accumulation that causes a health risk. A body mass index (BMI) $\geq$ 30 kg/m^2 is considered obese [19]. Among the well-established factors influencing obesity are the increase in the consumption of hypercaloric and nutritionally poor foods and a sedentary lifestyle. These often coexist with distress, hormonal imbalance, gut microbiome dysbiosis, poor sleep quality, or the consumption of certain medications, and can be boosted by genetic conditions [20]. The prevalence of obesity has risen dramatically worldwide in the last decades: in 2014, over 640 million adults had obesity, a six-fold increase since 1975 [19,21]. In addition, in 2016, over 124 million children and adolescents were obese [19]. These increments go hand in hand with the increased morbidity and mortality rate caused by cancer, and may be promoting obesity-related cancers at a younger age [22]. Currently, cancer is a leading cause of death worldwide, just behind cardiovascular diseases, and obesity is a major public health concern [19]. The association between obesity and cancer risk is supported by a large body of epidemiological evidence, which has been reviewed and meta-analysed by both the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) [23]. Adult body fatness has been established by the IARC as a strong risk factor for 13 different cancer types in humans, summarised in Table 1. In 2012, about 3.6% (481,000) of all new cancers (excluding non-melanoma skin cancer) in adults ($\geq$30 years old) were attributable to excess BMI (defined as 25 kg/m^2 or greater) [24]. In women, postmenopausal breast, endometrial and colon cancers accounted for 72.5% of the total attributable cases to high BMI, whereas in men kidney and colon cancers accounted for 66.0% [24]. Body fatness during childhood or early adulthood has also been associated with a higher risk of several malignancies in adulthood, including leukaemia, Hodgkin's disease, and colorectal cancer (CRC) [25,26]. For some cancer types, sex-related differences in association with obesity and cancer risk appear only later in life. An estimation of new cancers in the European Union using population-attributable risks showed that the incidence of new cancers attributable to excess weight (BMI $\geq$ 25 kg/m^2) was 2.5% for men and 4.1% for women, which suggested a higher risk of obesity-related cancers in adult women [27]. The WCRF/AICR made separate conclusions for body fatness in young women for breast cancer, owing to effect modification by menopausal status: they established that a 5 kg/m^2 increment in BMI probably decreases the risk of premenopausal breast cancer, whereas it increases the risk of post-menopausal breast cancer with a convincing level of evidence [23].

Table 1
Strength of evidence of the association between obesity and cancer risk.

Cancer site	Evidence for increased risk		Risk Estimate (95% CI)[a]
	IARC 2020	WCRF/AICR 2018	
Colorectum	Strong	Strong-Convincing	1.05 (1.03 – 1.07)
Endometrium	Strong	Strong-Convincing	1.50 (1.42 – 1.59)
Breast (post-menopausal)	Strong	Strong-Convincing	1.12 (1.09 – 1.15)
Oesophageal adenocarcinoma	Strong	Strong-Convincing	1.48 (1.35 – 1.62)
Kidney	Strong	Strong-Convincing	1.30 (1.25 – 1.35)
Liver	Strong	Strong-Convincing	1.30 (1.16 – 1.46)
Pancreas	Strong	Strong-Convincing	1.10 (1.07 – 1.14)
Thyroid	Strong	-	1.06 (1.02 – 1.10)[c]
Multiple myeloma	Strong	-	1.09 (1.03–1.16)[d]
Meningioma	Strong	-	1.54 (1.32 – 1.79)[b,e]
Gastric cardia	Strong	Strong-Probable	1.23 (1.07 – 1.40)
Ovary	Strong	Strong-Probable	1.06 (1.02 – 1.11)
Gallbladder	Strong	Strong-Probable	1.25 (1.15 – 1.37)
Prostate (advanced)	Moderate	Strong-Probable	1.12 (1.04 – 1.21)
Mouth, pharynx, and larynx	Moderate	Strong-Probable	1.15 (1.06 – 1.24)
Diffuse large B-cell lymphoma	Moderate	-	1.29 (1.16 – 1.43)[b,f]
Male breast	Moderate	-	1.19 (1.10 – 1.30)[g]
Cervix	Limited	Limited-suggestive	1.02 (0.97 – 1.07)

IARC: International Agency for Research on Cancer; WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research
Adapted from: World Cancer Report IARC 2020 [253] and Continuous Update Project Expert Report WCRF/AICR 2018[2]
[a]Risk Estimate (95%CI) for 5-unit increment in BMI (kg/m^2) adapted from WCRF/AICR [254] if not stated otherwise.
[b]Risk estimate (95%CI) for highest vs lowest category of BMI
[c]Source: Kitahara et al. 2016 [255]
[d]Source: Teras et al. 2014 [256]
[e]Source: Niedermaier et al. 2015 [257]
[f]Source: Castillo et al. 2013. Only in participants with obesity (BMI$\geq$30 kg/m^2) [258]
[g]Source: Brinton et al. 2014. [259]

3. Mediterranean diet and obesity-related cancers: epidemiological evidence

A growing body of evidence reinforces that an overall healthy dietary pattern, characterised by a low consumption of red and processed meats, high consumption of fruit and vegetables, whole grains rather than refined grains, and plant sources of protein and fat is inversely associated with the risk of cardiometabolic diseases and cancer [28]. At this point, there is solid evidence suggesting that a two-point increment of the MD score is associated with a 4% lower risk of cancer [29]. A recent meta-analysis including data from 3202,496 participants belonging to 117 studies (comprising randomised control trials, cohorts, and case-control studies), comprehensively examined the relationships between adherence to the MD and different cancer risks. As results, the authors showed that high adherence to MD is inversely associated with the risk of cancer mortality in the general population (Relative Risk (RR) = 0.87, 95% CI 0.82, 0.92), and all-cause mortality among cancer survivors (RR = 0.75, 95% CI 0.66, 0.86) [16] (Table 2). MD has been studied for its protective capacity against the risk of several obesity-related cancers, such as aerodigestive and gastrointestinal, gynaecological, and other cancers.

3.1. MD and aerodigestive and gastrointestinal cancers

Two different meta-analyses including data from case-control and prospective cohort studies showed that a high MD adherence was inversely associated with a 10–17% total risk of CRC [16,30], but not with total and CRC mortality [30] (Table 2). The protective effect of the MD against CRC was also observed in specific anatomical locations, including the proximal and distal colon, and rectum. Moreover, high

Table 2
Summary of results from last meta-analyses showing associations between Mediterranean diet adherence or olive oil intake and major outcomes of overall cancer and obesity-related cancer types in observational studies.

Cancer type/site	Outcome	Dietary factor (Highest vs Lowest)[a]	Number and design of studies	OR/RR (95% CI)	Reference
Overall	Cancer mortality	MD adherence	18 cohort	RR_{cohort} = 0.87 (0.82, 0.92)	Morze et al.[14]
Overall	All-cause mortality	MD adherence	8 cohort	RR_{cohort} = 0.75 (0.66, 0.86)	Morze et al.[14]
Overall	Cancer mortality	MD adherence	4 cohort	RR_{cohort} = 0.96 (0.82, 1.11)	Morze et al.[14]
Overall	Cancer reoccurrence	MD adherence	1 cohort	RR_{cohort} = 0.61 (0.18, 2.07)	Morze et al.[14]
Overall	Cancer incidence	OO intake	37 case-control 8 cohort	$OR_{case\text{-}control}$ = 0.65 (0.57, 0.74) RR_{cohort} = 0.90 (0.77, 1.05) $RR_{observational}$ = 0.69 (0.62, 0.77)	Markellos et al.[42]
Colorectal	Cancer incidence	MD adherence	7 case-control 10 cohort	$OR_{case\text{-}control}$ = 0.64 (0.52, 0.79) RR_{cohort} = 0.92 (0.87, 0.99) $RR_{observational}$ = 0.83 (0.76, 0.90)	Morze et al.[14]
Colorectal	Cancer incidence	OO intake	6 case-control 1 cohort	$OR_{case\text{-}control}$ = 0.91 (0.78, 1.06) RR_{cohort} = 0.88 (0.68, 1.14) $RR_{observational}$ = 0.90 (0.79, 1.03)	Markellos et al.[42]
Colorectal	All-cause mortality	MD $adherence_{prediagnosis}$ MD $adherence_{postdiagnosis}$	3 cohort 2 cohort	RR_{cohort} = 0.80 (0.62, 1.04) RR_{cohort} = 0.66 (0.37, 1.17)	Zhong et al.[18]
Colorectal	Cancer mortality	MD $adherence_{prediagnosis}$ MD $adherence_{postdiagnosis}$	3 cohort 1 cohort	RR_{cohort} = 0.90 (0.71, 1.14) RR_{cohort} = 0.84 (0.50, 1.42)	Zhong et al.[18]
Breast	Cancer incidence	MD adherence	11 case-control 12 cohort	$OR_{case\text{-}control}$ = 0.87 0.82, 0.93 RR_{cohort} = 0.97 (0.94, 1.00) $RR_{observational}$ = 0.94 (0.90, 0.97)	Morze et al.[14]
Breast	Cancer incidence	OO intake	11 case-control 3 cohort	$OR_{case\text{-}control}$ = 0.63 (0.45, 0.87) RR_{cohort} = 0.67 (0.29, 1.56) $RR_{observational}$ = 0.67 (0.52, 0.86)	Markellos et al.[42]
Breast	Cancer incidence	OO intake	8 case-control 2 cohort	$OR_{case\text{-}control}$ = 0.48 (0.09, 2.70) RR_{cohort} = 0.76 (0.54, 1.06) $RR_{observational}$ = 0.75 (0.56, 1.00)	Sealy et al.[43]
Gastric	Cancer incidence	MD adherence	3 case-control 4 cohort	$OR_{case\text{-}control}$ = 0.63 (0.53, 0.75) RR_{cohort} = 0.77 (0.64, 0.92) $RR_{observational}$ = 0.70 (0.61, 0.80)	Morze et al.[14]
Gastric	Cancer incidence	OO intake	3 case-control 1 cohort	$OR_{case\text{-}control}$ = 0.65 (0.46, 0.93) RR_{cohort} = 1.15 (0.78, 1.69) $RR_{observational}$ = 0.75 (0.53, 1.05)	Markellos et al.[42]
Pancreatic	Cancer incidence	MD adherence	1 case-control 3 cohort	$OR_{case\text{-}control}$ = 0.48 (0.35, 0.66) RR_{cohort} = 0.92 (0.81, 1.05) $RR_{observational}$ = 0.80 (0.60, 1.06)	Morze et al.[14]
Pancreatic	Cancer incidence	OO intake	1 case-control	$OR_{case\text{-}control}$ = 0.58 (0.35, 0.97)	Markellos et al.[42]
Liver	Cancer incidence	MD adherence	1 case-control 3 cohort	$OR_{case\text{-}control}$ = 0.51 (0.34, 0.77) RR_{cohort} = 0.67 (0.56, 0.80) $RR_{observational}$ = 0.64 (0.54, 0.75)	Morze et al.[14]
Esophageal	Cancer incidence	MD adherence	1 case-control 2 cohort	$OR_{case\text{-}control}$ = 0.26 (0.13, 0.52) RR_{cohort} = 0.85 (0.67, 1.09) $RR_{observational}$ = 0.64 (0.35, 1.16)	Morze et al.[14]
Esophageal	Cancer incidence	OO intake	3 case-control	$OR_{case\text{-}control}$ = 0.47 (0.24, 0.93)	Markellos et al.[42]
Head and neck	Cancer incidence	MD adherence	8 case-control 1 cohort	$OR_{case\text{-}control}$ = 0.54 (0.40, 0.72) RR_{cohort} = 0.73 (0.60, 0.89) $RR_{observational}$ = 0.56 (0.44, 0.72)	Morze et al.[14]
Aerodigestive	Cancer incidence	OO intake	6 case-control	$OR_{case\text{-}control}$ = 0.74 (0.60, 0.91)	Markellos et al.[42]
Endometrial	Cancer incidence	MD adherence	3 case-control 1 cohort	$OR_{case\text{-}control}$ = 0.58 (0.35, 0.95) RR_{cohort} = 0.98 (0.82, 1.17) $RR_{observational}$ = 0.67 (0.41, 1.11)	Morze et al.[14]
Ovarian	Cancer incidence	MD adherence	1 case-control	$OR_{case\text{-}control}$ = 0.91 (0.71, 1.17)	Morze et al.[14]

[a] Comparing highest vs lowest adherence or intake to Mediterranean diet or of olive oil, as appropriate. CI, confidence interval; MD, Mediterranean diet; OO, olive oil; OR, odds ratio, RR, relative risk.

adherence to the MD was associated with a lower overall gastric cancer risk [16,31], and by anatomical location (i.e., cardia and non-cardia) and histological subtype (i.e. intestinal and diffuse) [31,32]. A recent meta-analysis pooling data from one case-control and three cohort studies found that MD adherence was not statistically significantly associated with pancreatic cancer risk (RR = 0.80, 95% CI 0.60, 1.06) [16]. However, findings from two more recent prospective studies observed reductions for high MD adherence of between 18% and 43% in the risk of pancreatic cancer [33,34]. A high MD adherence was inversely related to liver cancer risk in a pooled analysis comprising data from one case-control and three cohort studies with a statistically significant risk reduction of 36% [16]. A similar association was observed in a prospective cohort study revealing that higher adherence to the alternate MD score was significantly associated with a lower risk of liver cancer [35]. A recently published meta-analysis encompassing data from one case-control and two cohort studies found no association between MD adherence and oesophageal cancer risk [16] (Table 2). To our knowledge, only one study has examined the association between MD and gallbladder cancer risk. The cohort study by Larsson et al. followed 76,014 subjects for 13.3 years and observed a significant reduction (Hazard Ratio (HR) = 0.42, 95% CI 0.23, 0.79) in gallbladder cancer risk in individuals following a high adherence to MD [36]. The MD has a beneficial role in the risk of head and neck cancer, which encompasses cancers in the oral cavity, pharynx, and larynx (all obesity-related cancers). Concretely, a recent meta-analysis showed that higher adherence to MD was related to a 44% lower risk of head and neck cancer [16] (Table 2). In summary, adhering to MD is associated with a lower risk of gastric, colorectal, liver, and head and neck cancers; while the results with pancreatic, oesophageal, and gallbladder cancer are still inconclusive.

3.2. MD and gynaecological cancers

Higher adherence to MD has been reported to be protective against breast cancer regardless of the menopausal status (i.e., premenopausal and postmenopausal) and hormone receptor expression (i.e., oestrogen, progesterone, human epidermal growth factor receptor (HER), and mixed) [16,37,38]. Likewise, greater adherence to the MD may positively impact on the quality of life of breast cancer survivors, specifically improving physical functioning, sleep, pain, and overall well-being [39]. A meta-analysis of three case-control and one cohort study by Morze et al., found no significant difference in endometrial cancer risk between low and high MD adherence [16] (Table 2). A prospective cohort study by Xie et al., explored the relationship between MD and ovarian cancer development in 82,948 women [40]. The results found that high MD adherence did not modify the risk of ovarian cancer among participants. Overall, the only gynaecological tumour where higher MD adherence is associated with lower risk is breast cancer.

3.3. MD and other obesity-related types of cancer

Only one study reported results on MD in relation to the risk of thyroid cancer. In a large prospective cohort, the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Llaha et al., mainly found no association between MD adherence and thyroid cancer risk [41]. Pooling data from two large prospective studies (N = 2792,257 person-years of follow-up, with 478 incident multiple myeloma cases), Lee et al., observed a suggestive inverse trend with multiple myeloma risk [42]. In another EPIC sub-study, a higher MD adherence was found to be modestly associated with the risk of overall lymphoma but not by subtypes, including diffuse large B-cell lymphoma [43]. To the best of our knowledge, there are no published studies on the relationship between MD adherence and the risk of other obesity-related cancers (namely thyroid, multiple myeloma, kidney, meningioma, and male breast cancer).

4. Olive oil and obesity-related cancers: epidemiological evidence

Olive oil is a key component of the MD and its consumption has largely been investigated concerning its capacity to reduce cancer risk. A recent meta-analysis of 37 case-control (17,369 cases and 28,294 controls) and eight cohort studies (12,461 incident cases in a total cohort of 929,771 subjects) concluded that higher OO consumption is associated with a 31% lower likelihood of any cancer (pooled RR = 0.69, 95%, CI: 0.62–0.77) [44] (Table 2). In the same meta-analysis, high OO consumption was inversely associated with the risk of oesophageal and breast cancers, but not with colorectal and gastric cancers [44].

4.1. Olive oil and aerodigestive and gastrointestinal cancers

Pooled data from observational studies support that high OO consumption may protect against upper aerodigestive (composed of oral cavity, pharynx, and larynx) and total gastrointestinal and oesophageal subtype cancer risk, but not against colorectal and gastric cancers risk [44] (Table 2). An Italian case-control study showed an inverse relationship between OO and pancreatic cancer [45]. To date, there are no previous publications on the relationship between OO consumption and the risk of liver, and gallbladder cancers.

4.2. Olive oil and gynaecological cancers

Breast cancer is by far the most studied gynaecological cancer in relation to the anticancer effects of OO consumption. Two recent meta-analyses of 10 (7030 cases among 81,436 participants) and 14 (29,830 cases among 987,895 participants) observational studies determined that women consuming higher amounts of OO reduced their risk to develop breast cancer between 25% (RR = 0.75, 95%, CI: 0.56, 1.00) and 33% (RR = 0.67, 95%, CI: 0.52, 0.86) compared with those consuming less [44,46] (Table 2). Contrary to breast cancer, evidence on endometrial and ovarian cancer is limited. Results from two case-control studies showed an inverse association between increased OO consumption and endometrial [47] and ovarian cancer [48] risks.

4.3. Olive oil and other types of cancer

As far as we know, there is no evidence regarding a potential relationship between OO consumption and the risk of other obesity-related cancer types, such as kidney, thyroid, meningioma, multiple myeloma, male breast, and diffuse large B-cell lymphoma cancers.

5. Obesity-related cancers' epidemiological evidence: strengths and limitations

Some limitations in methodological aspects may be behind the inconclusive results on the association between MD, OO, and several obesity-related cancers. For example, as stated in various systematic reviews and meta-analyses, two major limitations in most of these studies are inconsistencies in the definition of the MD pattern and the cut-off points used to differentiate high from low MD adherence [2,16,49,50]. To date, up to 34 different scores have been used in the literature to assess the degree of adherence to MD [51]. MD scores vary, especially as regards the inclusion or not of the alcohol component and the intake levels in the population. This variability might affect the results of MD and cancer relationships. Furthermore, the lack of information about the quality and safety (e.g., product treated or not with chemical agents, antibiotics, or hormones) of foods during the food intake assessment for MD scores could modify results, reducing the benefits of the MD [2]. Another common limitation may relate to dietary measurement errors, especially when dietary questionnaires are self-reported. Furthermore, dietary measurements are usually collected at baseline, which makes accounting for changes in diet during the follow-up not possible. On the

other hand, retrospective assessment of the usual diet, especially in subjects with the disease, as occurs in case-control studies, poses a high likelihood of recall bias and, hence, largely questioning its validity. Regarding OO, most studies acknowledge that they do not differentiate between common, virgin, and extra-virgin types. This distinction is important because compared to the refined type, VOO and EVOO have much higher concentrations of bioactive compounds and may, therefore, have more health benefits [52], including greater protection against cancer [53]. Finally, a higher adherence to the MD usually goes with a higher adherence to a Mediterranean lifestyle (e.g., healthier food preparation, eating locally and seasonally, socializing during meals, and even being more physically active and having an adequate rest) [1]. Although epidemiological studies often control for some of these factors, the presence of possible residual confounding cannot be excluded.

6. Obesity and cancer risk: biological mechanisms

The mechanistic pathways by which obesity is linked to carcinogenesis are not yet fully elucidated; current evidence suggests that several biological mechanisms might explain this association [54–56]. Here, we will focus on those related to chronic inflammation, insulin and insulin-like growth factor-I (IGF-I), sex hormone signalling, gut microbiome dysbiosis, and specific localised mechanisms. Fig. 1 summarises the mechanisms proposed and reflects how dysfunctional adipose tissue acts as one of the main triggers of these processes.

6.1. Chronic inflammation

Obesity is characterised by an excess of adipose tissue, an active organ with metabolic and endocrine activity, and is considered a low chronic inflammatory state [57]. During obesity, adipose tissue is characterised by infiltration of monocytes that switch to M1 macrophages, therefore, leading to dysfunctional adipose tissue [58]. These macrophages are often stimulated by cytokines such as interferon-γ (INF-γ) or by microorganism-associated molecular patterns (MAMPs) such as lipopolysaccharides (LPS) [59]. M1 macrophages alter the function of adipocytes, increasing pro-inflammatory cytokine secretion, including tumour necrosis factor-alpha (TNF-α), interleukin (IL)− 10 and IL-6, or monocyte chemoattractant protein (MCP)− 1 [55,58,60,61]. This leads to the production of free radicals and DNA damage, upregulation of proliferative and anti-apoptotic pathways, angiogenesis, and cell migration [61–63].

Adipokines (such as leptin and adiponectin) are adipocyte-derived hormones involved in metabolism regulation, crosstalk with inflammatory pathways, insulin signalling, angiogenesis, and cellular proliferation [57,64]. Leptin is an adipose-derived hormone linked to satiety and energy homeostasis control and its levels are increased in individuals with obesity. Mechanistic studies have shown that it increases angiogenesis, cell proliferation, migration, and invasion responses, as well as inhibition of apoptosis, which promotes cancer initiation and development [65–67]. A recent review of epidemiological and mechanistic studies linked higher levels of circulating leptin to breast, colon, thyroid, and pancreatic cancers [67,68]. Adiponectin, on the contrary, is produced only by mature adipocytes and its secretion is inhibited by insulin, its circulating levels are inversely correlated with the level of adiposity [69–71]. It has a potent anti-inflammatory effect, acting as an insulin sensitiser, which could indirectly prevent tumour development. In addition, a more direct effect is its ability to inhibit growth factor function (e.g., binding and sequestrating heparin-binding epidermal and basic fibroblast growth factors), decreasing cellular growth and proliferation, preventing DNA damage, and increasing apoptosis [55,70]. Several findings suggested a negative correlation between adiponectin levels and cancer risk, particularly via hormone-obesity-insulin resistance and suppression of growth and proliferation pathways [72]. Different mechanistic and epidemiological studies indicated that hypoadiponectinemia may be associated with the risk of different types of cancer, such as breast, endometrial, colon, gastric, pancreatic and haematological malignancies, among others [70]. In addition, chronic inflammation and oxidative stress, and abnormal secretion of adipocytokines have been included between the biological mechanisms that link

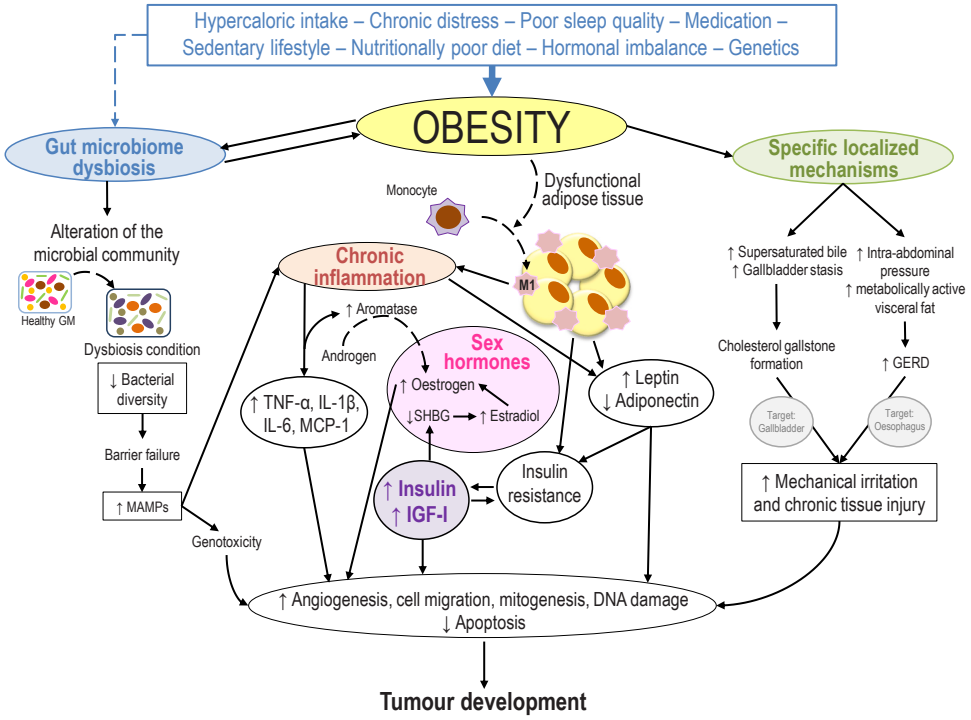

Fig. 1. Proposed mechanisms by which obesity may be linked to cancer risk. GERD, gastroesophageal reflux disease; GM, gut microbiome; IGF, insulin-like growth factor; IL, interleukin; MAMPs, microorganism-associated molecular patterns; MCP, monocyte chemoattractant protein; SHBG, sex hormone binding protein; TNF-α, tumour necrosis factor-alpha.

obesity with urinary cancers [73]. Local or systemic immune inflammation plays a role in the onset and progression of bladder cancer. During inflammation, the activation of inducible nitric oxide synthase (NOS) leads to the generation of nitric oxide, which can have several effects on bladder cancer development. Nitric oxide can impede DNA repair processes and promote angiogenesis, the formation of new blood vessels. N-nitrosamines, which are recognized bladder carcinogens in animals, can form within the bladder as a result of the interaction between oxidative byproducts of nitric oxide and secondary amines. This interaction may directly contribute to the initiation of bladder cancer [74].

6.2. Insulin and insulin-like growth factor I

Greater body fatness and altered adipocyte function is associated with higher circulating levels of insulin, and when body fatness is mainly distributed centrally, in the abdominal area, insulin resistance is more likely to develop [75]. Obesity-associated insulin resistance has been shown to be associated with elevated levels of pro-inflammatory cytokines, as a consequence of dysfunctional adipose tissue [58,76,77]. Chronic hyperinsulinemia may promote abnormal stimulation of multiple cellular signalling cascades, and increase the activity of IGF-I, a hormone primarily produced by the liver [78]. IGF-I binds to insulin receptors in different tissues and promotes cell proliferation, survival, migration, metabolism and angiogenesis, and decreases apoptosis, therefore, increasing the risk of different types of tumours [78–81]. Moreover, insulin decreases sex hormone-binding globulin (SHBG) levels, resulting in higher levels of free oestradiol and, therefore, oestrogen availability, thus increasing the risk of breast cancer [80]. Hyperinsulinemia and higher IGF-I levels have been clearly associated with the risk of breast, endometrial, ovarian, and prostate cancers and have been suggested to be involved in the development of several gastrointestinal cancers, thyroid cancer, and multiple myeloma in epidemiological studies [82–87]. In addition, they have been associated with increased pancreatic and breast cancer mortality [88,89], and overall cancer mortality [81,90,91].

6.3. Sex hormones

An increased dysfunctional adipose tissue leads to an increase in aromatase enzyme (also called oestrogen synthetase) expression and activity. Concretely, aromatase triggering may be induced by increased levels of adipose tissue TNF-α [92,93]. Aromatase is responsible for the conversion of androgens and androgenic precursors to oestrogens in adipose tissue. This production, together with decreased serum SHBG as a consequence of higher insulin and IGF-I plasma levels [80], increases the serum concentration of bioavailable oestradiol [94]. Oestrogens increase cell proliferation and reactive oxygen species and inhibit DNA repair machinery, leading to DNA damage and tumorigenesis [95]; it has been proposed as the mechanistic pathway linking obesity to postmenopausal breast and endometrial cancers [56,96–98]. Higher levels of oestradiol were associated with a higher postmenopausal breast cancer risk in a meta-analysis of eight prospective studies in postmenopausal women [94]. In addition, a review of epidemiological studies concluded that obesity class 1 (BMI>30 and <35 kg/m^2) was associated with a 2.6-fold increase in endometrial cancer risk, while obesity class 2 and 3 (BMI>35 kg/m^2) was associated with a 4.7-fold increase, when compared with women without obesity [99]. Sex hormones have also been implicated in the pathogenesis of urologic obesity-related cancers. Aromatase converts androgens into oestradiol, and, for example, enhanced prostate cancer risk has been associated with an increased oestrogen/testosterone ratio [73].

6.4. Gut microbiome dysbiosis

Recent research has demonstrated that obesity and its metabolic consequences are also related to alterations in GM and intestinal inflammation. GM dysbiosis can be a consequence of several factors, including antibiotic consumption, acute gastrointestinal infections, inflammatory bowel diseases, and diet [100]. Even so, obesity has been previously linked to GM dysbiosis [101]. GM dysbiosis is characterised by an imbalance between pathogens and natural and healthy microbiota, reducing symbionts (health-promoting) and increasing invasive, inflammation-inducing, genotoxic bacteria, and cancer-promoting metabolites [100]. The mechanisms linking obesity-associated GM dysbiosis to cancer development include altered microbial metabolism and generation of pro-carcinogenic metabolites, metabolic dysregulation, and induction of inflammation, as well as host immune response disturbance [102,103]. GM dysbiosis leads to a series of reactions that ultimately result in a cancer-promoting state with increased intestinal permeability. This phenomenon can be physical or at the level of antibacterial defence systems, and favour bacterial translocation [100]. This leads to increased inflammation, mediated by MAMPs, which activate macrophages and promote the secretion of pro-inflammatory cytokines [104,105]. GM dysbiosis can also result in genotoxicity mediated by bacterial genotoxins that induce DNA damage in organs in direct contact with the bacteria, like the gastrointestinal tract [103]. Microbial density is much higher in the gastrointestinal tract than in other organs and the occurrence of gastrointestinal cancers linked to GM dysbiosis is more likely than in other cancers [100,103]. For instance, dysbiosis, intestinal permeability, chronic inflammation, and bacterial genotoxicity were previously linked to CRC in mice [100]. However, the microbiota also mediates other pathways such as bile acids or oestrogen metabolism, and tumorigenic mediators that may exert long-distance effects, triggering tumorigenesis in organs with low or null microbial density, such as breast, liver, lung, or pancreas [100,106]. Dysbiosis of the gastrointestinal and urinary tract microbiome have been linked to higher risk of kidney and bladder cancers. An altered microbiome leads to a dysfunctional modulation of the endogenous anti-tumour immune response, as well as mucosa biofilm formation, pathogenic bacterial colonization, and induction of chronic inflammation via the reactive oxygen species molecular pathway among others [107,108].

6.5. Specific localised mechanisms

Obesity enhances hepatic secretion of cholesterol-supersaturated bile and gallbladder stasis, which may impact on cholesterol gallstone formation, increasing the risk of gallstone-related complications [109]. Gallstones produce mechanical irritation and delayed biliary emptying, resulting in dysplastic changes in the gallbladder [110]. In this sense, results from a recent meta-analysis of observational studies showed that the presence of gallstones is a major risk factor for gallbladder cancer (OR: 7.26; 95% CI: 4.33; 12.18) [111].

Obesity also increases the risk of oesophageal adenocarcinoma, an association that seems to be stronger than for other obesity-related cancers. A potential mechanism explaining this association is the increased occurrence of gastroesophageal reflux disease (GERD) [112]. High abdominal pressure caused by intra-abdominal adiposity relaxes the lower oesophageal sphincter, thus exposing the oesophageal mucosal to gastric content and irritating the mucosa. Recurrent exposure to gastric acid and chronic tissue injury can lead to Barrett's metaplasia and premalignant state [113]. In addition, increased metabolically active visceral fat leads to increased levels of adipokines, including IL-6 and TNF- α, which may also play a role in GERD and the consequent development of oesophageal cancer [114]. A meta-analysis of population-based studies showed that daily GERD symptoms presented a seven-fold increased risk of oesophageal AC (OR: 7.40; 95% CI: 4.94; 11.1) compared with participants without GERD or with less frequent symptoms [115].

6.6. Palmitic acid and tumour growth

Palmitic acid, a saturated fatty acid, has been investigated for its potential role in tumour progression and metastasis formation. Among the profound changes that occur to cells during development of cancer, lipid metabolism experiences a dramatic shift toward enhancement of lipid biosynthesis pathways. Increased lipid uptake, storage, and lipogenesis are strongly up regulated in tumour cells to maintain the structure and fluidity of cell membrane [116]. Studies on the molecular mechanisms underlying the effects of palmitic acid-derived metabolite on cell proliferation have suggested that the fatty acid possesses mitogenic activity upon exposure of fibroblasts to growth factors, even though the biological effect was not attributable to the free fatty acid itself but to a palmitoleic acid-containing inositol phospholipid species that accumulated in the cells upon cell activation. Palmitic acid can activate various signalling pathways within cells that are associated with cell proliferation, survival, and apoptosis resistance. One such pathway is the mammalian target of rapamycin (mTOR) pathway, which regulates cell growth and metabolism. Palmitic acid can stimulate mTOR signalling, leading to increased protein synthesis and cell proliferation. Moreover, excessive levels of palmitic acid can lead to the production of ROS, which can cause cellular damage and DNA mutation. Palmitic acid has been shown to induce epithelial-mesenchymal transition in certain cancer models, such as prostate cancer, where cancer cells lose their epithelial characteristics and acquire mesenchymal properties, facilitating their invasive and migratory capabilities [117].

Palmitic acid has also been linked to metastasis formation. It influences the expression of genes involved in cell adhesion, extracellular matrix remodelling, and metastatic colonization. One study in animal models observed that when oral tumour cells and melanomas from humans were exposed to a palmitic acid rich diet and transplanted into mice, they showed a greater capacity to metastasize, even when this diet was administered for a short period prior to the transfer [118]. Epigenetic modifications of metastatic cells caused by the fatty acid were permanent and cells maintained the most aggressive properties.

7. The effects of the mediterranean diet and olive oil on the biological mechanisms that link obesity and cancer

The Mediterranean diet has been linked to a decreased risk of various cancers associated with obesity. While the precise mechanisms remain incompletely understood, several potential pathways related to obesity have been proposed to mediate the favourable effects of the Mediterranean diet on cancer risk [2]. One such mechanism involves the anti-inflammatory properties of the Mediterranean diet [119]. As previously mentioned, obesity is linked to a condition of persistent low-level inflammation, marked by the secretion of pro-inflammatory cytokines and adipokines like interleukins, TNF-α, and leptin. These substances are produced by adipocytes in white adipose tissue and by inflammatory cells that infiltrate adipose tissue [120]. The Mediterranean diet, abundant in anti-inflammatory foods like fruits, vegetables, whole grains, and healthy fats such as olive oil, contains bioactive compounds such as polyphenols and omega-3 fatty acids that possess anti-inflammatory properties. By mitigating inflammation, the Mediterranean diet may lower the risk of obesity-related cancers. As mentioned, several types of cancer have been specifically related to obesity, where the immune and inflammation response produce cytokines and chemokines that enable cancer development, cellular proliferation, angiogenesis and modify tumour microenvironment [121]. This observation may provide a plausible explanation for the reduced cancer risk associated with the Mediterranean diet, which consists of foods possessing anti-inflammatory properties and other factors with potential anti-cancer effects. Furthermore, the Mediterranean diet's abundant antioxidants contribute to its anti-carcinogenic properties. Oxidative stress, implicated in cancer development, is counteracted by the antioxidants present in the Mediterranean diet. Components such as polyphenols found in fruits like grapes or extra virgin olive oil have been shown to possess anti-carcinogenic effects, including the inhibition of tumour growth and promotion of cancer cell death.

In addition, the Mediterranean diet's positive influence on insulin sensitivity and blood glucose regulation also plays a role in mitigating cancer risk associated with obesity. Through the consumption of fibre-rich foods, low-glycaemic carbohydrates, and healthy fats, the Mediterranean diet stabilizes blood sugar levels, improves insulin sensitivity, and potentially lowers the risk of obesity-related cancers. Higher adherence to a Mediterranean dietary pattern has been linked to improvement of insulin sensitivity and markers of inflammation (lower NF-κβ, higher adiponectin) in participants with overweight and obesity without diabetes [122].

Another significant mechanism that can contribute to the beneficial effects of the Mediterranean diet in obesity and related conditions is the modulation of gut microbiota composition [123]. Obesity alters the gut microbiota, contributing to chronic inflammation and metabolic dysfunction. The Mediterranean diet has been linked to a favourable profile of gut microbiota, primarily attributed to its high content of dietary fibre and bioactive compounds characteristic of a plant-based dietary pattern [123]. It may support a balanced immune system, improved nutrient absorption, and reduced inflammation, thereby impacting cancer risk, by generating metabolites through the fermentation of nutrients, particularly short-chain fatty acids [124,125]. The Mediterranean dietary pattern has been shown to be a major modulator of gut microbiota composition and metabolite production, related to the development of several intestinal and extra-intestinal diseases that may deriver on obesity-associated cancers such as colorectal cancer [126].

In summary, the beneficial effects of the Mediterranean diet on cancer risk, particularly in relation to obesity-related cancers, may be mediated through mechanisms such as anti-inflammatory effects, improved insulin sensitivity and glucose regulation, antioxidant properties, and modulation of gut microbiota composition.

8. Obesity and cancer: microbiota mechanisms

Among the biological mechanisms linking obesity and cancer, in this review, we will focus on those related to microbiota.

The bacterial profile of a "healthy" GM has not been defined yet [127–129], mainly due to the elevated inter- and intraspecific variability. It depends on age, sex, environment, and daily habits (e.g., diet, physical activity, and antibiotics), among others [127,130,131]. Each subject owns a unique fingerprint of microbiota and, perhaps, there is no single "healthy" GM profile. This is why the actual trends of nutritional interventions tend to be personalised [132–134], which explains why individuals following the same diet display very different responses [135,136]. GM, or more specifically, colon microbiota, is the most abundant and, probably, the most relevant in terms of physiological activity. It has been estimated that more than $3.9{\cdot}10^{13}$ microbial cells live in the human colon, which means that their proportion to human eukaryotic cells is 10:1 [137].

Factors that determine our microbiota's fate include some that have an effect even before birth [138]. Some of these, like inherited genetics, are nonmodifiable; however, other factors can be modified, such as the environment and the way we were born and fed during the first 1000 days of life [138]. Interestingly, the bacterial population of our microbiota strongly depends on the community where we live, such as rural, urban, industrialised, and non-industrialised areas [139]. Indeed, when we talk about the mechanisms that lead to the onset of cancer in individuals with obesity, we should consider that the direct cause is not due to alterations occurring in the microbiota or human cells alone, but in the cells and their environment as the holobiont [140]. Besides, the disequilibrium of the complex interactions maintained over time between microbiota and human cells causes health disorders and diseases [141].

The classic definition of obesity does not consider the metabolic

status of individuals. Therefore, when analysing GM in obese individuals, this differentiation should be considered [142]. In individuals with obesity, the GM proportion of the generally most abundant bacterial phyla is often altered, displaying a higher Firmicutes/Bacteroidetes ratio when compared with non-obese individuals. However, the opposite relationship has also been stated [143,144]. Remarkably, no differences were detected in the aforementioned ratio between obese subjects with and without metabolic syndrome [145]. An increase in Firmicutes levels is usually associated with a higher bacterial ability to extract energy from the diet, especially these rich in carbohydrates. This fact is associated with a boosted production of short-chain fatty acids (SCFAs) via saccharolytic bacterial fermentation [146]. Sometimes, this rise in SCFAs may also be due to diets high in fat and, particularly, saturated lipids. Unexpectedly, this could be a part of a compensatory mechanism to eliminate excess energy from the diet [147]. Another explanation of this process could be that the abundance of taxa related to SCFA production, such as the genera *Oscillospira* and *Clostridium*, was increased only in obese subjects without metabolic syndrome [145].

As stated by Crovesy et al., [144], Proteobacteria and Fusobacteria were also increased in subjects with obesity, probably due to a dysbiotic state. During dysbiosis, these phyla are found associated with opportunistic bacteria and low-grade inflammation. In contrast, the phylum Verrucomicrobia, with its best-known member *Akkermansia muciniphila,* tends to have a reduced abundance in obese subjects. Indeed, its high relative abundance is associated with a lower BMI and, therefore, its supplementation may improve some key metabolic parameters [144, 148,149].

8.1. Bacteria, obesity, and cancer… The good, the bad, and the ugly

Tumour development may be triggered either by dysbiotic imbalances of the bacterial community or the bacterial species themselves [150]. Some of these species, also called oncobacteria, are *Helicobacter pylori and hepaticus, Fusobacterium nucleatum, Streptococcus gallotycus* and *bovis, Enterococcus faecalis, Bacteroides fragilis,* and some pathogenic *Escherichia coli* strains [150,151]. The extensively studied type I carcinogen *H. pylori* causes gastric cancer in 3% of individuals in which this species is present [152].

Another concept that requires further research is the fact that microbiota can be found not only in the intestinal lumen and different areas in the body but also in tumours themselves. Even though bacteria can be found in tumours, their microbiota has remained unanalysed until recently [153]. Thanks to one of the pioneering studies regarding the microbiota in various tumour localisations, we know that the microbiota of each tumour type i) tends to be more similar to each other than to other types, iii) has distinct compositions at different taxonomic levels, and iii) can be differentiated based on their different bacterial communities [153]. In fact, using cancer tissues and blood samples, a microbiome-based diagnostic tool capable of discerning between individuals with or without cancer has been developed [154]. While, we currently do not know how to control tumoral microbiota, recent advances in the development of techniques to modulate it have been made, such as the use of genetically modified bacteria [155]. Besides, it is also essential to consider that bacteria are not the only members of the microbiota that have an impact on tumours, as an example, fungal composition is another emerging field. Recently, the finding of distinctive combinations of fungi in 35 cancer types was confirmed [156,157].

It is worth mentioning that GM can connect our digestive system with other parts of the body via both the circulatory and nervous systems, as it is densely vascularised and innervated [158], with a high presence of immune system cells [159]. Both translocation of gut-derived bacteria and MAMPs, which are also relevant to connect the gut lumen back with the rest of the body, are able to generate systemic inflammatory responses [160].

Until recently, GM was almost unexplored in other obesity-related cancers than those of the digestive system, despite the non-invasive nature of stool analysis. There are some cohort-like GM studies, such as the MetaHit European cohort [161], LifeLines-DEEP Dutch cohort [162], Spanish cohort [163], AWI-Gen South-African cohort [164] and Human Microbiome Project USA cohort [165], but they did not include the cancer perspective.

Studies comparing the GM in each type of obesity-related cancer vs. that in controls face the common limitation of non-easy comparability. GM cannot be analysed to draw conclusions without considering certain variables that affect healthy and sick individuals differently. Importantly, not all studies used the same statistical analysis and analytical methodologies. In CRC, GM may play an important role in its development [166–168]. Some cancer types, such as meningioma [169,170], thyroid carcinoma [171,172], kidney tumour [155], and multiple myeloma [173], have been recently analysed from a GM perspective, but the available evidence is still scarce and inconclusive. To our knowledge, there are no studies on other obesity-related cancers, such as oesophageal adenocarcinoma and gallbladder cancer.

8.2. Inflammation and bacterial metabolites

Although there are still many unresolved questions, there is a growing understanding of the impact GM may have on tumour growth and development. Faecal microbiota transplants provide strong evidence that GM can trigger obesity and/or cancer phenotypes [174–176]. Many systems are interconnected with the digestive system, so the mechanisms that are sometimes beneficial in one organ could favour tumour onset in another. In order to classify these mechanisms linking the microbiota to the establishment of obesity-related cancers, we will focus on the one hand, on those processes related to inflammation and, on the other, on those associated with the deregulation of metabolites of bacterial origin.

8.2.1. Inflammation

GM and host cells are in constant cross-talk, allowing the organism to detect any significant change that alters its correct function [177]. Various receptors, such as toll-like (TLRs) and nod-like receptors (NLRs), recognise the molecular patterns associated with the GM, thus maintaining a context-specific immune response [177]. In a healthy situation, a small amount of LPS derived from gram-negative bacteria passes into the bloodstream [178]. But if the LPS concentration in the blood increases, endotoxemia may occur and become serious because it is associated with the development of systemic inflammation [178]. As higher concentrations of LPS are often detected in subjects with obesity, their metabolism tends to be at a pro-inflammatory stage [179]. Endotoxemia also promotes diabetes, underlying the phenomenon of insulin resistance [178].

The increase in LPS concentration may be the consequence of several mechanisms. It could be due to the poor state of the intestinal epithelial barrier, which is covered by a mucous layer. Its regeneration is associated with a sufficient presence of *Akkermansia muciniphila* [180], bacteria usually present in lower concentrations in subjects with obesity. Tight junction proteins, such as zonulin and occludin, which are involved in the control of intestinal permeability (higher protein levels, higher permeability), are often increased in individuals with obesity [181,182]. LPS leakage involves the activation of, among others, TLR-4, triggering the activation of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) protein complex, which is usually involved in DNA transcription and whose hyperactivation is associated with the inhibition of apoptosis, promoting the release of various pro-inflammatory cytokines. The other mechanism likely to be behind the increase in blood LPS levels is related to the absorption of dietary lipids since, when chylomicrons, responsible for their transport to the liver, are formed, LPS sneaks in along with fats [178,183]. This mechanism triggers local macrophages and activates an inflammatory response, which, in turn, alters the metabolism of other specialised cells, such as liver Kupffer and stellate cells, activating

progressive processes that may eventually trigger cancer [178].

8.2.2. Dysregulation of bacterial metabolite production

In the microbiota-host relationship, bacteria are known for their ability to metabolise specific compounds from the diet, host cells, and the metabolism of other microorganisms, as well as, for producing essential molecules for health, such as vitamins B and K. However, they can also synthesise some compounds (SCFAs, secondary bile acids and trimethylamine) that can have harmful effects [184].

The GM may contain different bacteria with the ability to metabolise both the same and distinct compounds. Firstly, a number of genera, such as *Clostridium* and *Eubacterium,* are capable of transforming primary bile acids into secondary ones, such as deoxycholic and lithocholic acid, which are usually positively, but in some cases, negatively associated with tumours [185,186]. In obsess individuals, the metabolism of bile acids and GM change concomitantly [187]. Secondly, phosphatidylcholine-, choline-, and carnitine-fermenting bacteria metabolise trimethylamine from dietary origin substrates; trimethylamine is a precursor of trimethylamine-N-oxide (TMAO) and appears to be increased in some cancers, like CRC [188,189]. These bacteria mostly belong to the Firmicutes and Proteobacteria phyla, but not to Bacteroidetes [188]. A recent meta-analysis revealed a positive correlation between TMAO levels and BMI [190]. Thirdly, oestrogen-metabolising bacteria, known as the oestrobolome [191], interact with the inactive form of oestrogen, allowing it to be reabsorbed, increasing its serum levels and the risk of postmenopausal breast cancer [192]. It is worth highlighting that, during menopause, the synthesis of this hormone is transferred to the adipose tissue, which is increased in obese subjects [193]. Fourthly, SCFA-producing bacteria convert dietary fibre into SCFAs. These levels and their impact on health are sometimes controversial but, low SCFA concentrations are associated with higher CRC risk [194,195]. SCFA-producing bacteria are increased in metabolically healthy obese individuals but not in those with metabolic syndrome [145]; Finally, Sulphate-reducing bacteria, which can convert sulphur-containing substances into hydrogen sulphide (H_2S), and nitro-compound-producing bacteria, which synthesise N-nitroso compounds, nitroamides, and nitrosamines. Sulphate-reducing and nitro-compound-producing bacteria produce metabolites that are implicated in carcinogenic processes and are related to obesity since weight loss is associated with lower serum H_2S levels [196–198].

9. The effects of the mediterranean diet and olive oil on the microbiota that link obesity and cancer

In a previous review, our team explored the benefits of OO on the pathophysiology and incidence of cancer, placing special emphasis on the cellular processes involved in its benefits [50]. This current review aims to broaden this picture by the inclusion of the effect of both MD and OO on the GM and microbiota-related mechanisms that link obesity and cancer in humans. Despite not finding any specific studies on the effects of MD/OO on GM in humans with cancer, the evidence presented herein regarding patients with other diseases and healthy volunteers would serve as proof of concept for its potential cancer prevention.

9.1. Preclinical models

The lipid fraction found in OO (mainly monounsaturated fatty acids, but also polyunsaturated fatty acids and saturated fatty acids) and PCs, such as oleuropein or hydroxytyrosol, are noteworthy for cancer prevention. Their potential effects are being studied in vitro and/or in non-human animal models [166]. Among the fatty acids present in OO, oleic acid is the most abundant monounsaturated fatty acid. There is evidence from the 40 s regarding its positive effect on the growth of lactic acid bacteria [199]. More recently, its antibacterial activity has been proven in vitro and in vivo on the opportunistic pathogen *Staphylococcus aureus* [200]. Among polyunsaturated fatty acids, linolenic acid also presented an antibacterial effect in vitro and in vivo against *H. pylori* [201,202]. PCs have a direct prebiotic action, most of them reaching the gut untransformed, where GM enzymes make them partially bioavailable [203,204]. Dietary PCs and their associated metabolites may strongly influence GM composition, inhibiting harmful and stimulating beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* genera [166,203], and in some cases, also *Faecalibacterium* and *Roseburia* [203–205]. Similarly, in some of the studies summarised in Table 3 with MD and/or OO, the level of these taxa also increased, except for *Faecalibacterium* [206–211]. Conversely, some pathogens decrease in the presence of PC in vitro, such as *Staphylococcus aureus, E. coli* and *Listeria monocytogenes*, and there are beneficial species that also decrease, such as *Lactobacillus acidophilus* and *Bifidobacterium bifidum* [143].

9.2. Observational and interventional studies

In recent years, the modulatory potential effect of various food items on GM has been reviewed [212–214]. However, the isolation of the effects of a specific food within different dietary patterns is complex. An increasing number of studies support the benefits of MD in GM [206, 209,210,215,216]. The largest investigations regarding MD were the Prevention with Mediterranean Diet (PREDIMED) and PREDIMED-plus studies, in which the MD effect on GM was studied under particular conditions, such as insulin resistance or weight loss [216–218] (Table 2).

Regarding studies focused on MD, Haro et al., [206] analysed MD's effects in obese men in Spain. GM was found to be modulated by MD by decreasing *Prevotella* and increasing *Roseburia* and *Oscillospira* abundances; and, at the species level, *Parabacteroides distasonis* was increased. In another trial conducted in US healthy volunteers with a high risk of CRC [215], no differences were detected in bacterial abundance or diversity after an MD intervention. In a clinical trial conducted in Italy, after an MD including EVOO, the lactic acid bacteria abundance was higher in the overweight and obese compared with normal weight subjects and with pre-intervention [209] (Table 3). Later, in an observational study in Spain, levels of some beneficial bacteria increased in individuals with high MD adherence, such as *Bifidobacterium animalis,* but also some butyrate-producing ones such as *Roseburia faecis, Ruminococcus bromii*, and *Oscillospira plautii* [210]. In the PREDIMED-Plus study, both interventions, MD and a low-energy MD accompanied by exercise, produced GM changes in individuals with metabolic syndrome (with overweight or obesity) predominantly in the *Lachnospiraceae* and *Ruminococcaceae* families. In both interventions, the abundance of SCFA producers *Lachnospira* and *Lachnospiraceae NK4A136* was increased [216] (Table 3).

Few clinical studies specifically analysed the effect of OO on GM (Table 3) [207,208,211,219], but none were conducted in subjects with cancer. In the crossover study with hypercholesterolemia patients, three VOOs with different phenolic contents were compared. The most remarkable observation of this investigation was the increase in *Bifidobacterium* spp and *Parascardovia denticolens* after the VOO enriched with PC from thyme and OO (500 ppm), compared with the VOO intervention [207]. In another study, an intervention of EVOO consumption in men with undetectable human immunodeficiency virus (HIV) only affected bacterial diversity. In addition, several taxa showed changes at the genus and species level in the overall group and when sex was considered [208] (Table 3). In another trial carried out in overweight women from Brazil who followed an energy-restricted normal fat diet, EVOO consumption did not affect the diversity and relative abundance of GM [219]. In a trial with Chinese hypercholesterolaemia subjects, refined OO increased GM diversity and *Clostridium leptum* [211]. Interestingly, decreased GM diversity is not always an unhealthy sign; for example, a diet rich in EVOO has been linked to a significant reduction in GM diversity, causing a switch to a more protective group of bacteria in animal models [166].

While there is great variability in the results, most bacteria that

Table 3
The effects of MD and OO on GM in observational and interventional studies.

Reference MD	Subjects and Dosage	Methodology	GM changes	Other changes
Haro et al.[188] *CORDIOPREV*Spain	Interventional study with randomised obese adult men (n = 20)MD for one year	16 S rRNA sequencing Stool samples	↓ Prevotella ↑ Roseburia and Oscillospira↑ Parabacteroides distasonis	Changes in the abundance of 7 of 572 stool metabolites (amino acid, peptide, and sphingolipid metabolism associated)
Djuric et al.[197]*Healthy Eating Study*United States of America	Randomised, not-controlled, not-blinded trial with healthy adults with a high risk of colorectal cancer (n = 82)MD for six months	16 S rRNA sequencing Colonic biopsy samples	No significant differences in abundance nor in α-diversity	Bacterial communities differed by several parameters between subjects based on their serum carotenoids levels
Luisi et al.[191]Italy	Interventional study with overweight and obese adults (n = 18) and normal-weight control adults (n = 8) MD enriched with 40 g/day EVOO for three months	qPCR (primers for lactic acid bacteria) Stool samples	↑ Lactic acid bacteria	↓ Markers of inflammationand oxidative stress (subjects after vs. before intervention)↓ Proinflammatory cytokines (overweight and obese vs. controls)↑ IL-10 and adiponectin (overweight and obese vs. controls)
Rosés et al.[192] *Obekit*Spain	Observational study with normal weight, overweight, and obese adults divided by adherence to MD, high (n = 94) or low (n = 128)MD, with different adherence levels, for one year	16 S rRNA sequencing Stool samples	↑ Bifidobacterium animalis↑ Butyrate-producing taxa (Roseburia faecis, Ruminococcus bromii, and Oscillospira plautii)No species related to OO intake in high-adherence MD	
Muralidharan et al.[198] *PREDIMED-Plus*Spain	Randomised, controlled, parallel, not-blinded trial with overweight and obese adults with metabolic syndrome (n = 343)MD or energy restricted-MD with physical activity for one year	16 S rRNA sequencingStool samples	No significant differences in α-diversity↑ Lachnospira and Lachnospiraceae NK4A136↓ Butyricicoccus, Haemophilus, Ruminiclostridium 5, and Eubacterium hallii (in energy restricted MD compared to MD)↑ Coprobacter (in energy restricted MD vs. MD)↓ Haemophilus and Coprococcus 3 (associated with decreased adiposity parameters)↑ Lachnospiraceae NK4A136 (associated with adherence)	↑ in energy-restricted MD vs. MD:- Weight loss- Reduction in some parameters: BMI, fasting glucose, glycated haemoglobin, and triglycerides - HDL-cholesterol
OO				
Martín-Peláez et al.[189, 209]*VOHF*Spain	Randomised, controlled, double-blind, cross-over trial with adults with hypercholesterolemia (n = 12) 25 ml/day VOO (80 mg PCs/kg), FVOO (500 mg PCs/kg), or FVOOT (500 mg PCs/kg from OO and thyme) for three weeks for each oil type	Fluorescence in situ hybridization combined with flow cytometryStool samples	↑ Bifidobacterium and Parascardovia denticolens (in FVOOT compared to VOO)↑ IgA coated bacteria (in FVOO compared to baseline) not significantNo changes in Firmicutes/Bacteroidetes	↓ Oxidised LDL (FVOOT vs. baseline)↑ Protocatechuic acid (FVOOT vs. VOO)↑ Coprostanone (FVOO vs. FVOOT)↑ Faecal hydroxytyrosol and dihydroxyphenylacetic acids (FVOO vs. baseline and VOO)↑ CRP protein (FVOO vs. baseline, VOO, and FVOOT)
Olalla et al.[190]Spain	Interventional study with adults with HIV, aged ≥ 50 years with undetectable viral load (n = 32)50 g/day EVOO for 12 weeks	16 S rRNA sequencing Stool samples	↑ α-diversity (males)↑ Eggerthella, Ruminococcus, Lachnospiraceae, Parabacteroides, and Akkermansia (females)↑ Prevotella, Bacteroidetes, Bifidobacterium, Erysipelotrichaceae, and Eubacterium (males)↑ Gardnerella and Bulleidia moorei ↓ Mogibacterium, Dethiosulfovibrionaceae, Coprococcus, and some Bacilli species	↓ Total cholesterol
Netto Cândido et al.[201]Brazil	Randomised, parallel, double-blind trial with overweight adult women (total n = 52; EVOO n = 19)25 ml/day EVOO for nine weeks inside a breakfast drink with biscuits, inside an energy-restricted and normal fat diet	16 S rRNA sequencingStool samples	No significant differences in α-diversity nor richness (compared to baseline)No significant differences in abundance (in OTU, phyla, and genera levels; compared to baseline)	↑ Paracellular and transcellular permeability LPS concentrations remained unchanged
Lim et al.[193]Haldar et al.[203]China	Randomised, controlled, double-blind trial with adults with borderline hypercholesterolemia (total n = 146; ROO n = 44)30 ml/day ROO for eight weeks	16 S rRNA sequencingStool samples	↑ Clostridium leptum ↑ Veillonella, Clostridium, and Roseburia (negatively associated with pathological blood lipid parameters)	↓ Total and LDL-cholesterol, triglycerides, apolipoprotein B, ApoB/ApoA1 ratio and total cholesterol/HDL-cholesterol ratio

BMI, body mass index; CRP, C reactive protein; EVOO, extra-virgin olive oil; FVOO, functional virgin olive oil, FVOOT, functional virgin olive oil with thyme; LPS, lipopolysaccharide; MD, mediterranean diet; OO, olive oil; PC, phenolic compounds; ROO, refined olive oil; VOO, virgin olive oil;

became more abundant in both MD and OO trials were SCFA producers and particularly, butyrate producers [206–211,216]. From the studies that measured SCFAs in faeces, none detected changes in the fatty acid types tested [207,219]. It is striking that no SCFA changes were found linked to the increase in *Bifidobacterium* spp. [207], despite its known SCFA-producing capacity [220]. This finding underlines, once again, the complexity of GM modulation.

In these OO trials, its consumption could improve several cardiometabolic parameters, such as triglycerides, total cholesterol, cholesterol-associated LDL and HDL, and coprostanol [207,208,216, 221]. However, Luisi et al., found no differences after an MD with EVOO [209]. As cholesterol is the precursor of bile acids, the effects of OO on the above-mentioned metabolites, via the GM, could be beneficial. Interventions with OO in other clinical trials disrupted the levels of bile acid-related bacteria, *e.g.*, *Lachnoclostridium* and *Bilophila* [216], *Oscillospira* [210], and *C. leptum* [211].

There is scant evidence from trials regarding the effects of OO on either intestinal permeability or LPS. In a study with MD in high CRC-

risk subjects, LPS-binding proteins were less abundant in the group with higher serum carotenoid concentrations at baseline (which is negatively associated with CRC) [215]. In a Brazilian trial, paracellular and transcellular permeability were increased after EVOO intervention, although LPS levels remained unchanged in serum [219]. MD with EVOO, and also VOO interventions, can buffer LPS-associated endotoxemia [222,223] and prevent atherosclerosis, which is also linked to cancer [224] and both seem to be interconnected via the GM [225,226].

Both obesity and GM-associated endotoxemia aggravate processes related to systemic inflammation and oxidative stress, but OO has the potential to modulate both. Luisi et al., [209] found that the OO intervention affected both subjects with and without overweight/obesity, promoting a decrease in myeloperoxidase, 8-hydroxy-2-deoxyguanosine, and pro-inflammatory cytokines. IL-10 and adiponectin levels were also increased after OO intervention [209]. In another study by Martin-Peláez [227], the consumption of various VOOs did not cause any improvement in the variables associated with inflammation. They also pointed out that the use of pharmacological doses of a single source of PC increased the concentration of C-reactive protein, but this was not observed when two PC sources were combined. In another study, the decrease in C-reactive protein was associated with lower levels of Dethiosulfovibrionaceae [208]. Some of the GM modulations detected in this review, e.g., increased *Ruminococcus bromii, Roseburia genus, Clostridium leptum, and Bifidobacterium spp,* and decreased *Dethiosulfovibrionaceae*, including the compounds they produce, such as butyrate, have been associated with an anti-inflammatory effect [206–208,210,211]. The modulation of these bacteria is likely to be directed by fatty acids, as they have an antimicrobial effect, which in turn has an anti-inflammatory effect [219].

Insulin resistance is another metabolic complication frequently associated with obesity and inflammation. Interventions with OO and MD have been reported to reduce resistance, favouring sensitivity [206,209,210,215]. There are known negative associations with high serum carotenoid concentration [215], MD high adherence [210], and cytokines TNFα and IL-6 that impair insulin receptor signalling [209]. MD adherence increased insulin sensitivity and the *Roseburia* genus abundance in parallel, which is usually low in subjects with type 2 diabetes, suggesting a role in its prevention [206]. Some GM taxa associated with insulin resistance in non-diabetic subjects were reported in the PREDIMED-Plus study [218]. It is notable that the GM reported as beneficial for the insulin resistance stage, like *Oscillospiraceae*, had the same trend in some of the aforementioned studies [206,210].

10. Conclusions and future perspectives

We conclude that the current epidemiological knowledge shows associations between MD and OO consumption and most obesity-related cancers. In addition, the GM is involved in obesity-related cancers, and there are in vitro but also clinical studies that demonstrate that MD and OO can modify this microbiota. This microbiota modulation could play a role in the prevention and treatment of obesity-related cancers.

Primary cancer prevention involves adopting healthier lifestyle patterns, promoting greater physical activity and healthier food choices, and maintaining optimum body weight. In this context, the concept of "healthy lifestyle score" is gaining interest among researchers because the combination of various modifiable factors (i.e., smoking, BMI, physical activity, and diet), instead of dietary patterns alone, could lead to a greater reduction in the risk of many chronic diseases [228,229], including cancer [230]. It is important to bear in mind that MD has been included in most of the healthy lifestyle scores used today. We are convinced, therefore, that future research examining the relationship between the MD and olive oil adherence and cancer risk should integrate other factors of a traditional Mediterranean lifestyle, such as tobacco and alcohol consumption, physical activity, resting, and social activities.

In addition, microbiota modulation via the diet may play a role in cancer prevention and treatment. The symbiotic relationship between microbiota and the host must be seriously considered when studying human metabolism and obesity. Indeed, bacteria can be friend or foe since dysbiosis forms a part of carcinogenesis and, if we could achieve its correct management, we could decrease the cancer risk.

Given the unique characteristics of the microbiota and host, continued commitment is required for the personalisation of cancer management, both at the individual level and for different population clusters. Microbiota-based tools are being developed to facilitate the detection of different cancers [154,157]. Moreover, there is growing evidence that there is some inter-individual variability in the efficacy of anticancer treatments, and the consumption of probiotics [231] may increase their effectiveness [232–235].

Besides probiotics, there are others gaining importance: prebiotics, substrates selectively utilised by colonic microorganisms; synbiotics, a mixture of probiotics and prebiotics; and postbiotics, non-viable microorganisms and/or their microbial metabolites. Postbiotics have been around in Europe for some time; however, in the European Union, no specific regulation covers probiotics, prebiotics, synbiotics, or postbiotics [236,237]. Recently, in 2021, the use of *Akkermansia muciniphila*, known for its positive effects against obesity, was approved by the EFSA, as a novel food pursuant to Regulation (EU) 2015/2283 [238].

The classic, and often overlooked, way of modulating our microorganisms through diet and other habits also deserves a mention. As we have reviewed, both the MD and one of its main fats, OO, are involved in the relationship between GM and cancer. Furthermore, there are other dietary patterns, such as fasting-mimicking diets, ketogenic diets, and higher fibre diets, with this capacity [233]. A non-sedentary lifestyle and healthy lifestyle patterns associated with higher resting and less stress are other habits that should be considered [239–242]. It is also likely that, over time, other microbiota members, such as fungi (mycobiome) and even viruses (virome), will gain prominence and be analysed together in all those areas where the GM currently has a predominant role [243–245]. Therapies based on bacteriophage viruses are becoming increasingly more known [246,247].

Faecal microbiota transplants could become a fruitful modulatory tool of GM as some trials have already demonstrated [248,249]; indeed, they have usually been used to treat *Clostridium difficile*-resistant infections [250]. Another potential option that might seem like science fiction right now, is the use of models based on organ-on-a-chip, gut--microbiota-on-a-chip, and tumour-on-a-chip, which allows the design of prototypes more like humans, making them more applicable. Something yet more innovative about these chips is that they can be interconnected [251]. But if there is one thing that all these approaches have in common is that they will require the handling of a vast quantity of GM data combined with host metadata. This challenge can be tackled by omics technologies, such as microbiomics, nutrigenomics, and metabolomics. Collaterally, another indispensable tool for handling such complex data will be the use of artificial intelligence and machine learning techniques [252]. It is critical that both data and analytical tools be of open access so that researchers from any part of the world can benefit and contribute to these advances.

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CRediT authorship contribution statement

Conceptualisation, M.F.; methodology, E.A.-A., A.C., M.G.-L., N.B., R.Z.R., A.A., M.F.; software, E.A.-A., A.C., M.G.-L., N.B., M.F.; validation, M.F., A.C.; formal analysis, E.A.-A., A.C., M.G.-L., N.B., M.F.; investigation, E.A.-A., A.C., M.G.-L., N.B., M.F.; resources, R.Z.R., A.A., M.F.; data curation, E.A.-A., M.G.-L., N.B.; writing—original draft preparation, E.A.-A., A.C., M.G.-L., N.B., M.F.; writing—review and editing, R.Z.R., A.A., M.F.; visualisation, A.C., M.G.-L., N.B.; supervision, R.Z.R., A.A., M.F.; project administration, M.F.; funding acquisition, R.Z.R., A.A., M.F. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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