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Diet, menopause and the risk of ovarian, endometrial and breast cancer

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Abstract

Menopause, the permanent cessation of the menstrual cycle, marks the end of a woman's reproductive span. In addition to changes in sex hormone levels associated with menopause, its timing is another predictor of future health outcomes such as duration of the presence of vasomotor symptoms (VMS) and the risk of hormone-related cancers. With aging of the population, it is estimated that worldwide 1.2 billion women will be menopausal by the year 2030. Previously the effects of reproductive factors (e.g. parity, age at menarche, pregnancy) and socio-demographic factors on intermediate and long-term health outcomes of menopause have been widely documented. However, little is known about whether diet could have an impact on these. Therefore, we review current evidence on the associations of diet with menopause, presence of VMS and the risk of hormone-related cancers such as ovarian, endometrial and breast cancer. Dietary factors could influence the lifespan of the ovaries and sex-hormones levels, hence the timing of natural menopause. Few studies reported an association between diet, in particular soy consumption and a reduced risk of VMS. Sustained estrogen exposure has been associated with a higher risk of hormone-related cancers and thus high fat and meat diets have been linked with an increased risk of these cancers. However, to better understand the mechanistic pathways involved and to make stronger conclusions for these relationships, further studies investigating the associations of dietary intakes and dietary patterns with menopause, presence of VMS and the risk of hormone-related cancers are required.

Introduction - Menopausal transition and Menopause

Menopause, the last menstrual period, marks the end of reproductive life in women. With aging of the population, it is estimated that worldwide 1.2 billion women will be menopausal by the year 2030[1]. While menopause is inevitable, the age at which women reach menopause may vary depending on several factors such as geography and ethnicity. According to a meta-analysis of 36 studies (which included data from 35 countries), the overall mean age of natural menopause was 48.8 years (95% CI 48.3–49.2) with substantial geographic variation. For example, while the mean age of menopause in the United States (49.1y) and Asia (48.8y) were closest to the overall mean, it was higher in Europe (50.5y) and Australia (51.3y) and lower in Africa (48.4y), Latin America (47.2y) and the Middle East (47.4y)[2, 3].

At birth, the human ovaries contain approximately 1,000,000 primordial follicles[4]. This un-replenishable pool of follicles is further reduced to around 100,000 per ovary by the time of menarche. The fate of the remaining follicles is either to develop, reach maturity and then ovulate or degenerate by the process known as atresia[5]. At the perimenopausal transition stage, only about 100 to 1,000 follicles are left in each ovary and exhaustion of the follicle pool is accompanied by permanently elevated levels of pituitary gonadotrophins and the progressive reduction in antimullerian hormone (AMH) which confirms ovarian senescence[6]. The hypoestrogenic changes taking place during the perimenopause (menopausal transition) are a result of the interactions taking place between the hypothalamic-pituitary axis and the reproductive endocrine axis marking this irreversible decline in ovarian responsiveness[3].

The menopausal transition is the shift from normal reproductive life to the last menstrual period and can last for up to 10–15 years[7]. According to the Staging of Reproductive Aging Workshop[8], it is divided in two stages: early and late. The early menopausal transition is marked by changes in menstrual cycle length and is characterised by an increase in follicle-stimulating hormone (FSH) level, a decrease in AMH and inhibin B levels, while estrogen level remains stable. The late transition is marked by oligomenorrhea (infrequent periods) and can last for 1–3 years on average. This stage is accompanied by an increase in anovulatory cycles and also major fluctuations in hormonal levels. FSH level remains elevated while there is a consequent decrease in AMH and inhibin levels as well as estrogen level. After the final menstrual period, ovarian ageing is marked by a decrease in antral follicular count, and termination of ovulation and menstruation. In addition, there are further declines in AMH, inhibin and oestradiol levels[9, 10]. Ovarian ageing is also accompanied by loss of responsiveness to FSH and luteinising hormone (LH), hence causing a disruption in the negative feedback mechanism owing to the almost negligible inhibin level and decline in

estrogen level. Consequently, the production of gonadotropin-releasing hormone (GnRH) is upregulated, stimulating the release of FSH and LH. Thus, during the initial years after menopause the level of FSH peaks and gradually declines in the last postmenopause stage[3]. These hormonal fluctuations as a result of the neuroendocrine and reproductive endocrine interactions influence the risk of both intermediate and long term health outcomes associated with menopause[3]. One of the most common intermediate sequelae of the menopause transition, vasomotor menopausal symptoms (VMS), is defined as either the presence of hot flushes and/or night sweats. VMS is reported by 40-60% perimenopausal women and 8-80% postmenopausal women around the world[11]. The timing of onset of menopause can influence the length of the menopausal transition and hence the duration for the presence of VMS. Evidence also shows a link between an early onset of menopause and an increased risk of osteoporosis, cardiovascular disease, depression and mortality. On the other hand, a later age at menopause has been associated with a higher prevalence of hormone-related cancers such as breast, endometrial (uterine) and ovarian cancers[12]. Moreover, the presence of VMS has also been associated with an increased risk of cardiovascular disease[13]. Previous studies have demonstrated a link between reproductive factors, sociodemographic factors and the onset of natural menopause, presence of VMS and risk of hormone-related cancer[14, 15, 16]. However, its relationship with diet, a modifiable risk factor, has received less attention and current evidence of association is conflicting. Therefore, the aim of this review is to give an overview of the mechanistic pathway relating diet with age at natural menopause as well as to elucidate the relationship between diet and VMS (an intermediate sequelae of menopause) in addition to the risk of hormone-dependent cancers such as breast, endometrial and ovarian cancers (long-term outcomes of menopause) which are more commonly prevalent in developing countries.

Age at natural menopause

Natural menopause refers to cessation of the menstrual cycle without any surgical procedures such as oophorectomy or ovarian failure as a result of chemotherapy or radiotherapy[3]. A premature menopause is one which is reached before the age of 40 years, an early menopause between 40-45 years and a late menopause is one after the age of 55 years[17, 18]. Depletion of the ovarian reserve and its responsiveness to pituitary gonadotropins governs the lifespan of the ovary and thus influence the onset of the timing of the natural menopause[19]. Dietary factors and diet-related disorders can either enhance the lifetime of the ovaries by delaying follicular atresia or by maintaining sex-hormone levels involved in the feedback mechanisms of the menstrual cycle. However, the exact mechanisms still need to be elucidated. The association

of age at natural menopause with chronic disease, aging and general health makes it an important subject of clinical and public interest[12].

Metabolic disorders such as diabetes could accelerate reproductive ageing by causing premature ovarian failure through several mechanisms. This has been demonstrated in a study[20] including women from 11 Latin American countries. The author reported that diabetic women had an earlier menopause as opposed to non-diabetic women. Similarly, a recent study conducted in the Southern part of India demonstrated that an early menopause was more likely to be reported by diabetic women[21]. This is further supported by a British study which investigated the association between various food groups and the timing of the onset of natural menopause among 914 women in the Women's Cohort Study. It found that a high consumption of refined pasta and rice, high glycaemic index foods, were associated with an earlier onset of natural menopause[22]. Furthermore, findings from the prospective Nurses Health Study II demonstrated that a high vitamin D intake was associated with a lower risk of an early onset of menopause[23] which could be due to the fact that a high serum 25-dihydroxyvitamin D concentration could reduce the risk of diabetes as well as metabolic syndrome[24]. These findings thus indicate that the presence of type II diabetes, a diet-related disease could lead to an earlier onset of menopause.

Vegetarianism has also been linked to an earlier age at natural menopause[22, 25]. Vegetarian diets are usually characterised by a high dietary fibre and low fat content, particularly saturated fats. They tend to include more whole grains, vegetable protein sources such as legumes, nuts, and soy protein, and exclude red meat. Dietary fibre may potentially interfere in the enterohepatic circulation of sex hormones, by modifying the metabolic pathway of estrogens, leading to a decrease in estrogen bioavailability[12, 26]. Karelis et al.[27] demonstrated that vegetarians had higher levels of sex-hormone binding globulin (SHBG), higher total fibre intake as well as lower levels of free estradiol, free testosterone, dehydroepiandrosterone sulfate and a lower BMI. An intervention study, also reported that a change in fibre intake was significantly and independently associated with a decrease in serum bioavailable estradiol and total estradiol concentrations while no association was found between a change in fat intake and the hormone concentrations[28].

On the other hand, intakes of green and yellow vegetables as well as fresh legumes have been associated with a delayed onset of menopause[22, 29]. Ovarian ageing is closely associated with increased levels of reactive oxygen species (ROS) which arises mainly due to an imbalance between ROS production and non-enzymatic antioxidant defences[30]. Oocyte maturation, ovulation, luteolysis and follicle atresia are all affected by ROS[31]. Antioxidant properties of

foods have been found to be positively associated with a reduced rate of follicular atresia. A recent *in vivo* study demonstrated a reduced atretic follicle count with use of resveratrol (a polyphenol found in the skin of red grapes and berries)[32]. These contradictory findings could be because while few studies looked at the associations with dietary patterns, others considered the associations with individual food items. Moreover, differences in the participants' characteristics and distribution of age at natural menopause could further influence the findings. The confounders used in the analyses and large sample sizes could also explain the differences.

High consumptions of meat, fat, and protein have been positively associated with a delayed onset of menopause (Table 1). Cholesterol, the starting product of steroidogenesis can be synthesised by *de novo* synthesis in the endocrine tissue (e.g. granulosa-lutein cells in the ovaries) from acetate, the end-product of fat oxidation[33]. Therefore, an excessive dietary fat intake can result in higher serum estradiol levels. In addition, during the menopausal transition significant changes occurs in body composition. For instance, redistribution of body fat takes place such that there is an increase of total and central body fat, and also a redistribution of fat from lower body subcutaneous fat toward the abdominal region. This increase in adipose tissue becomes the main site for estrogen production along with other hormones such as leptin, adiponectin and resistin[34, 35]. Therefore, these endocrine changes taking place during the menopausal transition together with a high fat diet predisposes the woman to a later onset of menopause.

Menopause and its associated sequelae

The timing of menopause could determine the duration of the presence of VMS which is mostly prevalent during the perimenopausal years as a consequence of lowered estrogen levels (Figure 1). Previous randomised controlled trials have mainly focused on the study of phytoestrogen extracts and their influence on the presence of VMS. However, the study of foods consumed as part of the normal diet in relation to the presence of VMS has received less attention. The decline in estrogen levels during the menopausal transition is postulated to be one of the causes for the presence of VMS. A low estrogen level has been associated with narrowing of the thermoneutral zone between the core body temperatures, resulting in a lowered sweating threshold and hence a higher likelihood to experience hot flushes and night sweats. However, given that around 20% of premenopausal women also report hot flushes suggests that the decline in estrogen levels is not the sole endocrine change causing VMS[47]. Dhanoya et al.[48]

demonstrated that both AMH and FSH were associated with the presence of hot flushes while the level of oestradiol was not related with hot flushes.

Prolonged exposure to estrogens as a consequence of a delayed menopause increases the risk of hormone dependent cancers such as ovarian, endometrial and breast cancer as demonstrated previously by several epidemiological studies[49, 50, 51]. Other hormones such as progesterone may also be important. These hypotheses have been investigated in earlier published reviews[52, 53, 54]. Other factors such as diet (Figure 1), a modifiable risk factor may also explain the variation in estrogen and other sex hormones levels[55, 56, 57]. Diet-related pathologies may also promote tumorigenesis while some components of the diet may be protective against these cancers. Therefore, the next sections explore the evidence for the hypothesis that diet is a major determinant for the presence of VMS and for the risk of hormone-related cancers.

Presence of vasomotor symptoms

VMS such as hot flushes and night sweats are one of the most common symptoms experienced by women during the menopausal transition. The median duration of these symptoms is 4 years but may persist as long as 15 years for some women[47].

Evidence for a link between diet and presence of VMS arises from studies which have previously explored the associations between phytoestrogen extracts or phytoestrogen-rich foods and frequency or severity of VMS. A Cochrane review of 43 randomised controlled trials did not support the beneficial effects of phytoestrogen supplements for the reduction of the frequency or severity of VMS mainly due to the small size of the trials and also the high risk of bias while the same review stated the promising effect of genistein, a phytoestrogen found in soy[58]. A recent review further indicated the beneficial effect of isoflavones against hot flushes[59].

As mentioned previously, women tend to accumulate subcutaneous fat in the abdominal region during the menopausal transition which leads to endocrine changes in terms of higher circulating oestradiol level[34]. A prospective study of 6040 women demonstrated that a Mediterranean-style diet and a fruit rich diet were both inversely associated with VMS. On the other hand, diets with high fat and sugar contents increased the risk of VMS[60]. This could imply that a healthier diet which prevents obesity could also be protective against VMS. The same study reported that even after adjusting for BMI, the same associations were observed. Therefore, the mechanism involved between diet and presence of VMS still remains unclear.

Ovarian cancer

Women of reproductive age undergo cyclical cellular changes in their genital tract during the menstrual cycle[61]. During each cycle several follicles containing an ovum undergo a maturation and selection process where ordinarily one of them is selected and released from the ovary during ovulation on or around the 14th day of the cycle[62]. The menstrual cycle is under the influence of various hormones namely gonadotrophin releasing hormone, luteinizing hormone, follicle stimulating hormone, estrogen, and progesterone[63]. During ovulation the surface of the ovary ruptures to release the ovum, following which the cells on the surface of the ovary, known as the epithelial cells, proliferate to close the breach under the influence of estrogen. Improper proliferation of those cells can result in formation of cysts or even cancers like surface epithelial tumours which are a sub group among the diverse types of ovarian tumours[64].

Estrogen and progesterone are steroid hormones synthesised from cholesterol[33]; individuals having a high fat diet provide the substrate for excessive estrogen synthesis which stimulates cell proliferation in the female genital tract. Diets high in animal protein also contains xeno-estrogens which have carcinogenic potential[65]. Leptin, another hormone secreted by the adipose tissue under the influence of factors like high lipid levels in blood, has several effects on the body like producing a feeling of satiety, as well as stimulating the release of GnRH which in turn stimulates release of LH and FSH[66]. High levels of LH may result in the immature release of the ovum and high levels of estrogen secondary to high circulating cholesterol levels in the body (as a result of high saturated fat and energy intake). Consequently, this may result in improper re-epithelialisation of the ovaries. Chronic stimulation of ovaries in this way may predispose to development of abnormal growths which subsequently can undergo malignant transformation. Therefore, diets high in energy, fats, or animal protein may promote development of ovarian cancer.

Omega-3 fatty acid, a polyunsaturated fatty acid (PUFA) can be obtained through dietary sources (flaxseeds, walnuts, canola oil, and oily fish) only. The n-3 family of PUFAs comprises alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). According to *in vivo* studies, EPA and DHA have been found to be precursors for anti-inflammatory lipid mediators[67]. Estrogen has proliferative effects on estrogen-sensitive tissues and thus could be involved in the pathogenesis of some hormone-dependent cancers such as ovarian cancer. Dietary n-3 PUFAs deter the promotion and progression stages of carcinogenesis through several mechanistic pathways. One of the mechanisms involves

changes in estrogen metabolism which could result in reduced estrogen-stimulated cell growth [68, 69].

Prostaglandin E2 (PGE2), an arachidonic acid (an n-6 PUFA found in meat and fish)-derived eicosanoid stimulates the activity of aromatase P450, which converts 19-carbon steroids to estrogens while on the other hand, PGE3 (derived from EPA metabolism), does not activate aromatase P450. Hence, an increased intake of EPA, which leads to increased production of PGE3 and decreased production of PGE2, is expected to decrease estrogen production and thus reduce estrogen-stimulated cell growth[68]. In addition, n-3 PUFAs can influence the regulation of two transcription factors; sterol regulatory element binding protein-1c (SREBP-1c) and peroxisome proliferator activated receptor alpha (PPAR alpha). SREBP-1c is involved in inducing a set of lipogenic enzymes in liver and n-3 PUFAs can potentially inhibit the expression and processing of SREBP-1c and thus inhibits the de novo lipogenesis of fatty acids, making it an important consideration for the carcinogenesis. Merritt *et al.* [70] demonstrated that a higher intake of omega-3 may be protective for ovarian cancer, while a greater consumption of trans-fat was associated with an increased risk of ovarian cancer. However, the clinical effects of n-3 PUFAs does not solely rely on its concentration alone, but most importantly on the ratio of n-3 PUFAs to n-6 PUFAs in the cells[71]. For instance, in a study using a knockout mouse model it was demonstrated that a dietary ratio of omega-6/omega-3 PUFA lower than 5 was effective in suppressing tumour growth, and prolonging animal lifespan[72]. Thus, a high intake of n-3 PUFAs relative to that of n-6 PUFAs may decrease endogenous estrogen production and reduce the risk of ovarian cancer.

Along with hormonal control, diet can also interfere at the level of fatty acid (FA) and cholesterol biosynthesis and eventually affect sex steroid metabolism and thus risk of ovarian cancer[73]. For instance, it has been found that feeding previously fasted animals a diet high in carbohydrate and low in fat content causes a dramatic induction of enzymes such as fatty acid synthase (FAS) and mitochondrial glycerol-3-phosphate acyltransferase (GPAT) which are involved in FA and triacylglycerol (TAG) synthesis. FAS and GPAT are the two critical enzymes involved in FA and TAG biosynthesis. FAS catalyses the synthesis of long-chain fatty acids, primarily palmitate, using acetyl-CoA and malonyl-CoA as substrates and NADPH as the reducing equivalent while GPAT catalyses the first committed as well as the rate-limiting step in TAG and phospholipid biosynthesis[74].

Dietary variations are responsible for fluctuations in nutrient intake which can result in changes in circulating glucose, which in turn signal the secretion of hormones. For example, ingestion of a high-carbohydrate diet leads to a high circulating insulin level which consequently induces

enzymes involved in FA and TAG synthesis, thus providing FA for membrane phospholipid biosynthesis in cancer cells. On the other hand, during a state of fasting or starvation, glucagon level is elevated which suppresses activities of enzymes involved in FA and TAG biosynthesis by increasing the intracellular cAMP level[73, 74, 75]. Moreover, *in vivo* studies have demonstrated that high carbohydrate and low fat diets lead to higher rates of lipogenesis than diets rich in fat and low in carbohydrates. The type of carbohydrate also affects lipogenesis such that diets with fructose as the primary source of carbohydrate cause higher rates of FA synthesis and higher activities of the lipogenic enzymes than diets containing equivalent amounts of glucose[76].

Endometrial cancer

As mentioned previously, the cells in the endometrium undergo cyclical cellular changes during the menstrual cycle. Hormones like estrogen have a mitogenic effect on the cells of the endometrium[77, 78]. Excessive exposure to estrogen either exogenous or endogenous secondary to high fat diet may cause increased proliferation of the endometrial cells. Cells proliferating at a faster rate are more prone to errors during DNA replication and the mutated cells can subsequently undergo malignant transformation, most commonly adenocarcinomas.

Endometrial cancer is a hormone-driven cancer, with approximately 80% of endometrial cancers potentially arising due to either an excess of estrogen or a lack of progesterone. In the normal endometrium, the proliferative effects of estrogen are normally countered by progesterone, but the absence of progesterone allows estrogen to induce oncogenesis, an effect that is amplified in situations of excess estrogen (Figure 1). One of the major emerging causes of the estrogen/progesterone imbalance is obesity which is known to influence hormonal balance and level of growth factors[79, 80]. Evidence shows a positive link between increased dietary fat intake and obesity, thus associating fat intake to an increased risk of endometrial cancer[81]. Central obesity, characterised by high abdominal fatness is commonly observed among women during the menopausal years and is responsible for the increase in circulating free fatty acids and consequently promotes an increase in insulin resistance[82]. In addition, long-term consumption of high glycaemic index diet is another risk factor for obesity and insulin resistance and is also hypothesised to be involved in the pathogenesis of endometrial cancer[83]. Hyperinsulinaemia increases the risk of endometrial cancers mainly by the binding of insulin to insulin receptors on endometrial cells to stimulate the growth of endometrial stromal cells as well as through other pathways[77].

Breast cancer

The pathogenesis of breast cancer is intricate and multifactorial. The aetiology of breast cancer could include mutation in the BRCA1 gene, a family history of breast cancer or mutagens which can lead to DNA damage. It can also involve a similar hormonal pathogenesis as ovarian cancer[84]. Importantly, estrogen influences growth, differentiation and functioning of the breast tissue (Figure 1). Aromatase, an enzyme found in the adipose tissues helps convert circulating cholesterol to oestradiol[85]. Due to the higher proportion of fat cells in breasts of older women, their level of oestradiol in the breast tissues particularly post menopause is likely to be higher than the plasma circulating level. The high oestradiol level in the breast tissues can trigger differential effects on the estrogen receptor expression which are found in those tissues, thus influencing the behaviour of cancer cells[86]. Stromal cells in the breast tissues can also support metastatic activity as they do not only control growth of normal breast epithelial cells but also that of neoplastic epithelial cells by secreting growth factors in response to the levels of endogenous hormones[87].

High cholesterol level, as a result of a high fat diet has also been stated as a risk factor for breast cancer among women during the late peri-menopausal and post-menopausal state[88]. According to studies in mice[89, 90], oxysterol 27-hydroxycholestrol (27-HC), a metabolite of cholesterol synthesis has been identified in the pathogenesis of breast cancer. 27-HC could stimulate the growth of breast cancer cell lines by binding and activating estrogen receptors (ER) in a similar way as oestradiol. There is also evidence that postmenopausal women experience an increase in their cholesterol level and thus its metabolite 27-HC which could help explain the increase in breast cancer risk among obese and hypercholesteraemic women[91]. However, according to a recent EPIC-Heidelberg Cohort study publication including 530 incident cases of breast cancer, a high level of 27-HC was associated with a reduced risk of breast cancer among postmenopausal women and no association was found among premenopausal women[92].

Moreover, a fat-rich diet is positively correlated with insulin resistance[93]. Insulin resistance, a major factor in the pathogenesis of premenopausal breast cancer, is also involved in the aetiology of postmenopausal breast cancer. Insulin can bind to insulin receptors found on the epithelial cells of the breast. This insulin signalling can contribute to cancer through mitogenic activity mediated by the phosphatidylinositol-3 kinase and mitogen-activated protein kinase/Akt signalling pathways[94]. Insulin also has anti-apoptotic characteristics and thus promotes tumour invasive activity. Insulin resistance is also accompanied by high levels of proinflammatory cytokines and leptin as well as a decreased level of adiponectin which

concomitantly lead to both ER-positive and ER-negative breast cancer[95]. Moreover, insulin resistance is associated with an increased estrogen level as a result of enhanced aromatase activity and decreased production of SHBG[96, 97]. This mechanistic pathway has been supported by by an Italian-nested case-control study which demonstrated that both pre- and post-menopausal women with hyperglycaemia had an increased risk of breast cancer[98].

In addition to the high circulating level of estrogen as a result of obesity, the associated high levels of inflammatory markers, insulin-like growth factors and adipokines from the visceral fat also increases the risk of breast cancer among postmenopausal women[99]. While high circulating estrogen level among premenopausal women can be a risk factor for breast cancer[100], some studies have demonstrated that obesity can be protective among premenopausal women. Obesity can lead to irregular ovarian cycles and hence lower circulating estrogen levels. As demonstrated by a meta-analysis of prospective studies, waist circumference was associated with ER-positive and progesterone receptor positive breast cancers in postmenopausal women while in premenopausal women waist circumference was positively associated with ER-negative breast cancer[101]. This would suggest a lower likelihood of a hormonal pathogenesis for breast cancer among premenopausal women. Chronic inflammation, abnormally high levels of insulin-like growth factor (IGF) and insulin resistance have been linked to premenopausal breast cancer[102].

Other protective effect of diet against the risk of hormone-dependent cancers

Vitamins like B_6, B_{12} and folate are required for normal DNA repair mechanisms and proper DNA replication. Folate receptor alpha expression is correlated with stage and grade of ovarian cancer, suggesting this pathway may be relevant to ovarian carcinogenesis and progression[103]. Ascorbic acid, vitamin E and other trace elements like selenium having antioxidant properties help to protect from free radical injury and maintain normal cellular function. Vitamin C is recognised for its beneficial effect in cancer chemoprevention mainly as it has the potential to stimulate immune function, impede nitrosamine formation, minimise DNA damage and block the metabolic activation of carcinogens[104]. Vitamin A helps to control epithelisation of tissues and also has antioxidant properties to help protect from DNA damage[105]. Although these current theories support the plausible role of these micronutrients in hormone-dependent cancer, prospective studies as well as a recent pooled analysis of cohort studies and meta-analyses reported no association between dietary vitamins A, C or E and the risk of ovarian

and endometrial cancers[104, 106, 107, 108]. In addition, the WCRF/AICR[82] reported inconclusive association between nutrients such as vitamin A, C, E as well as folate and the incidence of ovarian, endometrial, breast cancers.

Moreover, a recent meta-analysis of cohort and case-control studies suggested that vitamin D intake was protective against premenopausal breast cancer[109]. A large cohort study including 68,567 postmenopausal women further demonstrated that women with a high intake of calcium, and vitamin D had a reduced risk of postmenopausal breast cancer[110]. Experimental studies have also suggested that vitamin D intake could reduce the stimulatory effect of androgen in human ovarian cancer cell lines and also reduce obesity induced endometrial cancer[111, 112]. However, systematic reviews concluded that the evidence to support the association between vitamin D intake and endometrial and ovarian cancers are not consistent and strong, thus calling for further prospective studies. One of the limitations was that since most of the studies included in this systematic review were case-control studies, diet was thus measured only at 1-time period and was very prone to misreporting due to recall bias, therefore not accounting for diet change over time and vitamin D production through the skin[113, 114].

Flavonoids, a group of heterogeneous polyphenols, have multiple health benefits. The main sources of flavonoids include fruits, vegetables, tea, and wine[115]. Flavonoids reportedly have several properties which contribute to the various health benefits including antioxidant, anti-mutagenic, and anti-proliferative properties. Among them, isoflavones and some flavones, flavanones, and flavanols also have estrogenic or anti-estrogenic activity, which makes these compounds of particular interest for modulation of reproductive cancer risks[116]. According to a large prospective cohort study including 171,940 US women, 723 of whom developed ovarian cancer over a period of 16–22y of follow-up, demonstrated inverse associations between flavonol and flavanone intakes and ovarian cancer risk[117]. Further supporting the chemoprotective role of the flavonol in ovarian cancer risk, two *in vitro* studies demonstrated that kaempferol induces apoptosis in ovarian cancer cells by regulating pro-apoptotic and anti-apoptotic protein expressions and by preventing angiogenesis in ovarian cancer cells[118, 119]. Furthermore, a meta-analysis of six cohort and six case-control studies demonstrated that intakes of flavonols and flavones are protective against breast cancer, especially among postmenopausal women[120], thus supporting the chemo-preventive role of fruits and vegetables in hormone-related cancers.

Recommendations and future research based on the current evidence

In summary, evidence shows that diets predisposing to obesity and insulin resistance are the main drivers of sex hormone fluctuations among both pre- and post-menopausal women. Fluctuations in estrogen levels have been associated with the timing of the onset of natural menopause, the presence of VMS, and longer-term sequelae such as ovarian, endometrial and breast cancer. Studies have demonstrated that both the consumption of more balanced diets, rich in fibre, fruits and vegetables (and, by contrast, those less healthy containing processed meats and rich in fat) can alter circulating levels of estrogen and other sex hormones. Diet could consequently influence the timing of natural menopause and hence affect its associated sequelae. However, further evidence around the hypothesis that diet might influence timing of menopause and presence of VMS are required in observational trials and use of metabolomics may be valuable in revealing mechanistic pathways. Additional observational studies may also clarify the association between diet and hormone-related cancers.

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Conflict of interest

JEC is a director of the University of Leeds spin out company Dietary Assessment Ltd.

Authorship

Y.D. drafted the manuscript. J.E.C and D.C.G critically revised the manuscript for important intellectual content. All the authors have read and approved the final manuscript.

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Table 1. Evidence for the associations between diet and onset of menopause

Author, year	Study Design, sample size	Intervention/exposure	Findings	
			Early	Late
Torgerson et al., 1994[36]	Cross-sectional, 2,074	Meat, alcohol	-	Meat Alcohol
Torgerson et al., 1997[37]	Prospective, 1,227	Meat, alcohol	-	Alcohol
Nagata et al., 1998[38]	Cross-sectional, 3,704	Total energy; macronutrients; cholesterol; calcium; crude fibre; vitamins A, C, D, and E; carotene; soy product; retinol; coffee; alcohol	Soy products Coffee	Fat Cholesterol
Nagata et al., 2000[29]	Prospective, 1,130	Energy, macronutrients, animal protein/fat, vegetable protein/fat, fat from fish, cholesterol, calcium, crude fibre, vitamin A, retinol, vitamin C, vitamin E, green and yellow vegetables, other vegetables, soy products	-	Green & yellow vegetable
Nagel et al., 2005[39]	Prospective, 5,568	Macronutrients, alcohol, meat, dairy products, fish, vegetables, fruit, cereal products, fibre, soy products, sweets, added animal fat, added vegetable fat	Carbohydrate Vegetable Fibre Cereal products	Total fat Protein Meat
Martin et al., 2006[40]	Randomised clinical trial, 2,611	Low-fat high-carbohydrate diet	-	-
Dorjgochoo et al., 2008[41]	Prospective, 33,054	Energy, macronutrients, vegetables, fruit, red meat, saturated fat, total soy, total fibre, tea, alcohol	-	Energy Fruits Protein Carbohydrate
Nagata et al., 2012[42]	Prospective, 3,115	Energy, total fat, SFAs, PUFAs, MUFAs, long omega-3 FAs, dietary fibre, soy isoflavones, alcohol	Polyunsaturated fat	-
Carwile et al., 2013[43]	Prospective, 46,059	High-fat dairy, total low-fat dairy, skim milk, whole milk, dairy fat, dairy protein, calcium, vitamin D, lactose	-	Low fat dairy Skim milk
Purdue-Smithe et al., 2017[23]	Prospective, 116,430	Vitamin D, calcium intake from dairy and non-dairy sources		Vitamin D from dairy sources Calcium from dairy sources

Boutot et al., 2017[44]	Prospective, 85,682	Vegetable protein, animal protein, total protein, all meat, red meat, processed meat, chicken/turkey, seafood, eggs, soy/tofu, beans/lentils, peanuts, peas/lima beans, other nuts, peanut butter, pasta, dark bread, cold cereal	-	Vegetable protein Pasta Dark bread Cold cereal
Wang et al., 2018[45]	Cross-sectional, 17,076	Meat, seafood, fresh eggs, soybean products, fresh fruits, dairy products, vitamins, minerals	Seafood Fresh eggs Fresh fruits Vitamins	Meat
Dunneram et al., 2018[22]	Prospective, 35,375	Wholegrain products, refined grain products, low-fibre breakfast cereals, high-fibre breakfast cereals, plain potatoes, potatoes with added fat, refined pasta and rice, wholegrain pasta and rice, low-fat dairy products, high-fat dairy products, butter and hard margarine, margarine, low-fat spreads, high-fat dressing, low-fat dressing, soya bean products, textured vegetable protein, pulses, eggs/egg dishes, fish & fish dishes, oily fish, shellfish, red meat, processed meat, poultry, offal, vegetables, fruits, dried fruits, other foods groups, tea, coffee, soft drinks, wines, spirits, beer and cider, port/sherry/liqueurs	Refined pasta and rice	Oily fish Fresh legumes Vitamin B6 Zinc
Purdue-Smithe et al., 2018[46]	Prospective, 116,429	Low-fat dairy foods, high-fat dairy foods, total dairy	-	Total dairy Low-fat dairy foods

Figure 1: Potential mechanistic pathways though which diet can influence circulating estrogen levels and women's reproductive health