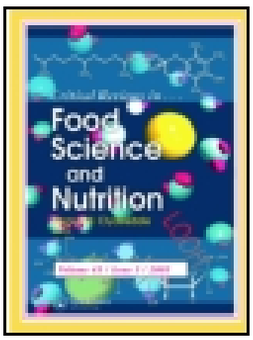

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Impact of consumption of repeatedly heated cooking oils on the incidence of various cancers- A critical review

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Abstract

Repeated heating of vegetable oils at high temperatures during cooking is a very common cooking practice. Repeatedly heated cooking oils (RCO) can generate varieties of compounds, including polycyclic aromatic hydrocarbons (PAH), some of which have been reported as carcinogenic. RCO is one of the commonly consumed cooking and frying medium. These RCO consumption and inhalation of cooking fumes can pose a serious health hazard. Taking into account exploratory study, the present review aims to provide the consumption of RCO and its fumes cause the high incidence of genotoxic, mutagenic, tumorogenic and various cancers. The information on RCO and its fumes were collected through a library database and electronic search (ScienceDirect, PubMed, and Google Scholar). Remarkable studies demonstrated that the health adverse effects of RCO and its cooking fumes have been often attributed to their detrimental properties and ease to genotoxic, mutagenic and carcinogenic activities. RCO and its cooking fumes were found to enhance the incidence of aberrant cells, including breaks, fragments, exchanges and multiple chromosomal damages and micronuclei in a dose-dependent manner. Furthermore, the large consumption of RCO has been associated with a number of malignancies, including lung, colorectal, breast, and prostate cancers. The present review provides additional insights into the polluting features of PAHs produced various cancers via cooking activities in indoor environments.

Keywords

Repeatedly heated vegetable oils; polycyclic aromatic hydrocarbons; genotoxicity; mutagenicity; carcinogenicity; cancers

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Abbreviation

AGEs advanced glycation end products

ALA alpha-linolenic acid

ALP alkaline phosphatase

AST aspartate transaminase

ATP adenosine triphosphate

BMI basal metabolic index

CI confidence interval

CVD cardiovascular diseases

DHA docosahexaenoic acid

DNA deoxy ribonucleic acids

FFA free fatty acids

GC-MS gas chromatography- mass spectroscopy

GGT gamma glutamyl transferase

GLA gamma-linolenic acid

GPx glutathione peroxidase

GSH glutathione

GSR glutathione reductase

GST glutathione-s-transferase

HCA heterocyclic amines

HPLC high performance liquid chromatography

IFN interferon

IL interleukin

MDA melondialdehyde

MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

MUFA monounsaturated fatty acids

NF-κB nuclear factor kappa B transcription factor

OR odds ratio

PAH polycyclic aromatic hydrocarbons

PCa prostate cancer

PCNA -proliferating cell nuclear antigen

PM particulate matter

PUFA polyunsaturated fatty acids

RCO repeatedly heated cooking oils

ROS reactive oxygen species

TBARS thiobarbituric acid reactive substances

TGF transforming growth factor

TGL triglycerides

TUNEL terminal deoxynucleotidyl transferase dUTP nick end labeling

UV ultra violet

VEGF vascular endothelial growth factor

VEGFR vascular endothelial growth factor receptor

Introduction

Vegetable oil is one of the main dietary components in the day to life food consumption and is used in nearly all types of food preparations including frying, baking, sauteing, dressing, marinating, and extrusion cooking. They are generally obtained from oil seeds (i.e. mustard, sunflower, cottonseed, corn, and coconut), food legumes (i.e. soybean, peanut), nuts (i.e. almond) or the soft substances of fruits (i.e. olives). They are primarily composed of triglycerides and serves as main sources of fat consists of three fatty acids and one molecule of glycerol (Sayon-Orea et al., 2015). The minor components are free fatty acids, fat-soluble vitamins, pigments, phospholipids, waxes, sterols and fatty alcohols. Vegetable oils contain different kinds of fatty acids and their compositions are widely varied; however, one type of fatty acid is generally predominant over the other fatty acids. The chief fatty acid in olive oil is oleic acid, monounsaturated fatty acids; and the predominant fatty acid in sunflower oil is linoleic acid, polyunsaturated fatty acids (Foster et al., 2009). Physical and chemical characteristic features of vegetable oils are influenced by the quantity of fatty acid and the place, where they positioned on the glycerol (American Oil Chemists' Society, 2006).

Deep frying of vegetable oils is one of the most common methods of food preparation worldwide. The practice of reusing oils for repeated frying is also common in an attempt to cost-effective. When oils are used in frying, the temperature ranges between 170^{o} to 220°C and it undergoes physicochemical changes such as oxidation, hydrolysis, cyclization, and polymerization and eventually, it degrades to volatile compounds (Ku et al., 2014). These repeatedly heating alter manifestation of the oil with high viscosity, color darkening, froth and smoke point reduction, which makes more harmful when these oils consume along with the food. Many studies showed that the reheated oils cause genotoxic (Dung et al., 2006), mutagenic and carcinogenic potential (Srivastava et al., 2010a, 2010b). Further, the studies demonstrated that the deleterious health effects of consumption of reheated oil cause increased blood pressure (Psaltopoulou et al., 2004; Leong et al., 2009; 2012), cardiovascular diseases (Ng et al., 2012; 2014a, 2014b), atherosclerosis (Adam et al., 2008), endothelial dysfunction (Lopez-Garcia et al., 2005), impaired vasorelaxation responses (Owu et al., 1997), hypertension (Soriguer et al., 2003) and elevated LDL, and lipid peroxidation (Siti et al., 2008).

2. Nutritional and health benefits of cooking oil

Cooking oil is a crucial part of our day to life in the diet possess the primary sources of lipid, which gives energy (9 calories/gram) to the human and a chief ingredient of biomembrane (Vaskova and Buckova, 2015) and building blocks of many lipid hormones (Falade et al., 2017). In addition, the nutritional and health benefits of these cooking oils are massive and this can be endorsed to their individual ingredients such as fatty acids in the amount of saturated to unsaturated fats; and monounsaturated to polyunsaturated fats. In addition, these fatty acids possess an assortment quantity of natural antioxidants such as vitamin A, E, and carotenoids that protect cells from free radical damage and to prevent the incidence of oxidative rancidity in the frying oil (Fahy et al., 2009).

Polyunsaturated fatty acids (PUFAs) are present in excellent quantities in vegetable oils such as sunflower oil (Das, 2008) and offer as major integral part in mitochondrial membranes. The effectiveness of electron transport system is terminated due to the inadequacy of PUFA. PUFA, in general, are anti-atherogenic properties that reduce serum cholesterol and triglycerides (Endo and Arita, 2016). The biological importance of prostaglandins, thromboxanes, and leukotrienes are produced by arachidonic acid, one of the major PUFA constitutes 10–15% of the total fatty acids in the membranes. Generally, PUFAs enhances cementing constituents and fluidity in the membrane and protects the cell. Docosahexaenoic acid (DHA) is usually synthesized by alpha-linolenic acid (ALA), another chief PUFA that found in soybeans, flax seeds, walnuts, and spinach (Lv et al., 2016). Gamma-linolenic acid (GLA) prevents CVD through expanding the blood vessels, lowering BP, and avoids the occurrence of atherosclerosis (Kitamura et al., 2011).

In addition, GLA inhibits the augmentation of tumors and various cancers. The dietary sources of GLA are primarily obtained from plant seed including primrose, black currant, and borage. Biologically significant PUFAs are eicosapentaenoic acid (EPA) and DHA synthesized from ALA, jointly called as omega-3 fatty acids. The main sources of ALA in the diet are walnuts and hazelnuts (Calder, 2012). Intake of these omega-3 fatty acids is clinically important, which reduces the activities of white blood cells and generate mediators of inflammation. Furthermore, they reduce the ability of blood platelets to release thromboxanes and stimulate the

blood clotting mechanism. Hence, omega-3 fatty acids serve as the precursors for potent anti-inflammatory lipids (Anand et al., 2008), powerful cell signaling role and thus acting as a reservoir of the biomolecules (Healy et al., 2000).

Monounsaturated fatty acids (MUFAs) are chiefly present in the vegetable oil such as peanut oil, mustard oil, olive oil and canola oil (Guthrie and Pcciano, 1995), which prevents coronary heart disease (Hu and Willett, 2002). It is well known to have a favorable effect on the blood lipid profile and thus reduce the risk of CVD (Demonty et al., 2006; Metcalf et al., 2007). In addition, these fatty acids are less likely to react with ROS and more stable in oxidative stress settings when compared with PUFA (Diniz et al., 2004). However, the experimental studies associations between dietary consumption of MUFAs and risk of coronary heart disease have been still uncertain (Jakobsen et al., 2004).

3. Deep fried cooking oil

Frying is a commonly employed method for preparing food as it can make the food very appetizing and aromatic, which provides delicious taste. The common issue raised in cooking oil nowadays is repeatedly heating and used it over several times. This practice may not be regular in residential cooking, however, it is more common in hawkers which can aid them to reduce their expenses and earn more income. Normally, cooking oil can be obtained from plant or animal sources. The most commonly used cooking oils are peanut oil, corn oil, palm oil, coconut oil, sunflower oil, and lard. During cooking, hydrolysis of oil occurs in the beginning when moist food is fried in hot oil. This reaction enhances the acid value of oil because of fatty acid production from triglycerides. Oxidation of oil during frying is the key of concern. Oxidation occurs due to reaction with the atmospheric oxygen. Auto-oxidation can also occur though the oil is not heated, this process is supported by external temperature or exposed to UV light (Gotoh et al., 2007). Three phases that occur during oxidation of oil are initiation, propagation and termination phases (Gotoh et al., 2007). These processes generate more free radicals such as lipid peroxides, PAH, aldehydes, ketones, alcohols, and acids (Romero et al., 2006; Choe and Min, 2007). Oxidation mechanism is more prone to occur in unsaturated fatty acid compared to saturated form (Mensah and Obeng, 2013). When the oil is heated, thermal dissociation occurs in unsaturated fatty acid containing double bonds, which allows removal of the hydrogen atom to

form alkyl radical or lipid radical and this process occurs in initiation phase (Gotoh et al., 2007, Good, 2012). In the propagation phase, unstable lipid radical become more unstable free radicals; they are generally called as peroxy lipid free radicals. In the termination phase, unstable two free radicals react and form non-radical species (Romero et al., 2006). The physicochemical changes during thermal oxidation of cooking oils are depicted in **Table 1.**

4. Generation of carcinogenic agents and fumes

Frying is a process that persuades a multitude of biochemical reactions in the hot medium and produces an abundance of chemical compounds (Belitz et al., 2004). These degraded compounds may include FFA, aldehydes, alkanes, 4-hydroxy nonenal, hydro-peroxide volatile compounds, and polymerized triglycerides (Choe and Min, 2007). The quantities of degraded products elevate with the length of heating time at high temperature. Thus, the more the oil is heated, the more deprivation takes place and the more noxious compounds and lipid peroxidation products are formed in the cooking oil (Lapointe et al., 2006; Romero et al., 2006). Several factors can influence the quality value of cooking oil during heating, including aeration, temperature, duration of the heating, the type of oil, the saturation ratio of the oil, and the presence of a catalyst (Gupta, 2005; Falade and Oboh, 2015). The degree of changes in the physicochemical properties of the oil dictates the quality of the oil for human consumption.

Research studies have indicated that RCO is generally used 3--6 times before being discarded as waste (Mensah and Obeng, 2013). RCO lowers the smoke point, which is the temperature at which the oil breaks down creating acrolein, an obnoxious smelling compound; and visible cooking fumes are produced (Good, 2012). In addition, almost sixteen PAHs were recognized in fumes released during deep-frying of rapeseed, soybean, peanut, and olive oil (Yao et al., 2015). Furthermore, Li et al. (1992) also recognized five PAHs (benzo(a)pyrene, dibenzo(a,h)anthracene, benzo(a)anthracene, dibenzo(a,b)anthracene, and benzo(e)pyrene) in six cooking oil fumes. Zhao et al. (2006) also found that cooking oil increases lung cancer susceptibility in China due to frequent deep-frying fumes and deprived ventilation in kitchens. Chen et al. (2012) also identified 21 PAHs and Jørgensen et al. (2013) found 32 PAHs from deep-frying oil medium. In addition, Dost and Ideli (2012) identified 9 PAHs in fumes produced when meat and fish were roasted using three different edible oils. See and Balasubramanian

(2008) also examined the chemical characteristics of fine particulate matter (PM2.5) emitted when plain tofu was cooked using various cooking methods with cooking oil. The list of PAHs in cooking oil fumes (Li et al., 1992; 2003; Chen et al., 2012; Yao et al., 2015) are depicted in **Figure 1**.

PAHs are organic compounds, containing two or more fused benzene rings composed of hundreds of chemical groups (Abdel-Shafy and Mansour, 2016), and they are consistent organic pollutants exhibit teratogenic, genotoxic (Srivastava et al., 2010a, 2010b), carcinogenic (Sinha et al., 1999; Ramesh et al., 2004; Pandey et al., 2006), and mutagenic effects in living organisms (Wornat et al. 2001; Dung et al., 2006). Increase in mutagenicity is proportionally related to its frying time (Chen et al., 2003). Humans are exposed to PAHs largely through breathing and ingestion (Chen et al. 2012), and these PAHs threaten human health to cause lung, stomach, esophagus, and skin cancers (Wu and Yen, 2004; Li et al. 2011). Pandit et al. (2001) also reported that RCO generates a diversity of volatile, semi-volatile, and particulate matters. The epidemiological study was done by Lopez- Abente et al. (2001) suggested that people exposed to PAH are at the risk of developing cancers. Another epidemiological study has also indicated that a high intake of RCO containing saturated fat increases the risk of cancers (Houthuijzen, 2016).

Degraded compounds from RCO may form DNA adducts, which have been proposed as predictive biomarkers of human cancers (Korsh et al., 2015). Results of this study revealed the presence of six times higher amount of total PAH in RCO compared with the fresh cooking oil. The greater amounts of PAH are reported to have significant carcinogenic and mutagenic potential (Isidori and Parrella, 2009), which are dependent on the number of cycles used for heating (Pandey et al., 2006). The genotoxicity and carcinogenicity assays performed to detect both the chromosomal aberration and micronuclei induction in the bone marrow (Shukla et al., 2003).

By using these two assays in this study, RCO was found to enhance the incidence of aberrant cells, including breaks, fragments, exchanges and multiple chromosomal damages and micronuclei in a dose-dependent manner. Chromosomal aberration and micronuclei induction by PAH (Shukla et al., 2003) are well documented. The results of this study also suggest that RCO

may contain a high amount of PAH (Marsili et al., 2001). Repeatedly heated cooking oil emits PAHs and subsequent causes of cancer are depicted in **Figure 2**.

5. Mutagenicity and genotoxicity effect of PAHs in RCO

Benzo[a]pyrene was classified as group 1 carcinogens (IARC 2012); dibenz[a,h]anthracene was originally classified as "probable" human carcinogens (2A); whereas, naphthalene, benzo(a)anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-cd]pyrene were deemed of "possible" human carcinogens (2B) (IARC 2010). Dibenzo[a,h]anthracene was detected in nearly all samples collected in peanut and olive oil cooking fumes. Regarding "possible" human carcinogen (2B) compounds, naphthalene, benzo(a)anthracene were found in all the samples collected in cooking fumes. Indeno[1,2,3-cd]pyrene and benzo[b]fluoranthene were observed in all deep-fried food samples.

PAHs are highly lipid soluble and thus readily absorbed in the gastrointestinal mammals. They are rapidly distributed in a variety of tissues with the marked tendency for localization in body fat (Abdel-Shafy and Mansour, 2016). These carcinogenic PAHs are genotoxic and induce mutations that initiate cancer. These progressions of cancer chemically induce by enzymes in metabolites that react with DNA, leading to mutations. When the DNA sequence is altered in genes that regulate cell replication, cancer can result. PAHs can bind to DNA at specific sites, forming bulky complexes called DNA adducts that can be stable or unstable (*Henkler et al., 2012*). Stable adducts may lead to DNA replication errors, while unstable adducts react with DNA strand, removing a purine base (*Henkler et al., 2012*). Such mutations if they are not repaired, can transform genes encoding for normal cell signaling proteins into cancer-causing oncogenes (Baird et al., 2005). Low molecular weight PAHs are more potent as co-carcinogens during the promotional stage of cancer. In this stage, first cells are removed from growth suppressing signals from its neighboring cells and begin to clonally replicate (*Ramesh et al., 2004*). Low molecular weight PAHs that have bay or bay like regions can dysregulate gap junction channels, interfering with intracellular communication, and affect mitogen-activated protein kinases that activate transcription factors involved in cell proliferation (*Ramesh et al., 2004*).

The bulk intake of these fried foods has been related with various malignancies, including colon, rectum, breast, kidney and pancreas cancers (Gonzales et al., 2014). These malignancies may be due to the reduction of omega-3: omega- 6 proportions, and intake of frying oil by-products (Ansorena et al., 2010). The bulk consumption of fried food was related with a 1.3- to 2.3-fold increased risk of prostate cancer (Li et al., 2014; Stott-Miller et al., 2013). *In-vitro* and *in vivo* genotoxicity and mutagenicity effect of RCO are depicted in **Table 2.**

6. Tumorigenic effect of PAHs in RCO

Extensive and systematic animal studies on the tumorigenicity effect of PAH, possess diol epoxides, which are main mutagenic and carcinogenic species (Conney et al., 2001). These metabolites are effectively changed by epoxide ring by electrophilic carbonium ions that strongly bind to nucleophilic sites of DNA and in proteins. Furthermore, these oxidative metabolites produce BaP-7, 8-dihydrodiol-9, 10-epoxide (BPDE) from BaP-7,8-dihydrodiol and found in almost all tissues, while examined. This metabolite is the only isomer with high tumorigenic potential and is the predominantly bound to DNA (Conney et al., 2001). *In vitro and in vivo* studies have also shown the cytotoxicity effect of BaP. Various other PAHs cause very severe, long-lasting hyperplasia and other adverse effects similar to the neoplastic changes (Charles and Adaku, 2010). In addition, BaP and various other PAHs administered through oral cause tumors in the forestomach, lungs, liver, pancreas, and breast of rodents, while mono- and dinitro pyrenes also cause tumors in breast and pituitary (Imaida et al., 1991). The impacts of the tumorigenic effect of RCO are depicted in **Table-3.**

7. Impact of RCO on various cancers

The impacts of covalent binding of PAHs to DNA in the various tissues of rodents have been extensively studied in *in vivo* and *in-vitro* (Boström et al., 2002). Experimental animal studies have demonstrated that (+)-anti-BPDE-DNA adducts are the primary adducts formed in lung, liver, heart, pancreas, stomach, skin and kidney. However, the studies using systemic administration in rodents, the quantities of DNA adducts were higher in liver, lung, and spleen. On the other hand, DNA adducts were lower in kidney and stomach (Ross et al. 1990, 1991; Rojas et al., 2001; Pauk et al., 2013). According to the epidemiological studies, DNA adducts and its several factors associated with an increased risk of cancer and are related with high risk

of atherosclerosis. This is because of somatic mutation involved in the formation of the atherosclerotic plaque (Pulliero et al., 2015). PAHs, including dibenz[a,h]anthracene, dibenz[a,c]anthracene, 7,12-dimethylbenz[a]anthracene and BaP, were shown to act as initiators and/or accelerators of various cancers in chickens, pigeons and mice (Wakabayashi, 1990). Newborn mice are very susceptible to the carcinogenic action of PAHs. When the administration of BaP and other PAHs in rats through intraperitoneal or subcutaneous cause liver and lung tumors within 6 months (Platt et al., 1990). In addition, nitro-PAHs cause leukemia, breast and colorectal cancer (Imaida et al., 1992). Intrapulmonary injection of BaP and other PAHs also produced lung tumors in rats and hamsters (Hartung et al., 1990). However, the significance of this pathway for PAH carcinogenicity in experimental animals and humans are as yet unclear (Cavalieri and Rogan, 1996). The impacts of RCO on various cancers are depicted in **Table-4.**

7.1. Lung cancer

The basis of the epidemiological studies, cooking fumes exposure to women from cooking oils showed to be a primary risk factor for various cancers including lung cancer (Purcaro et al., 2006; Yao et al., 2015). A study in Taiwan associated with three different cooking oils and their fumes were analyzed. Various PAHs including (benzo(a)pyrene (B(a)P), benz(a)anthracene (B(a)A), and dibenz(a,h)anthracene (DB(ah)A) were detected in all samples. A concentration of DB[a,h]A and B[a]A were 1.9 and 2.2 µg/m^3 in fumes from lard oil, 2.1 and 2.3 µg/m^3 in soybean oil, 1.8 and 1.3 µg /m^3 in peanut oil, respectively. Benzo[a]pyrene (B[a]P) was identified in fume samples of soybean and peanut oil, in concentrations of 19.6 and 18.3 µg /m^3 respectively. This experimental observation concluded that women exposed to the emitted fumes of RCO are at increased risk of lung cancer (Chiang et al., 1997). Earlier studies have also suggested a positive correlation between the emitted fumes of RCO and high risk of lung cancer (Wu et al., 1998; Purcaro et al., 2006; Yao et al., 2015). Another investigation related to population-based case-control study among Chinese women in Shanghai, there was an increased risk of cancer in mammary gland related with high intake of deep-fried red meat (OR = 1.92; 95% CI, 1.30–2.83) and deep-fried fish (OR = 1.52; 95% CI, 1.05–2.22) (Dai et al., 2002). Consumption of these deep-fried food has been highly connected with the risk of pancreatic (Ji et

al., 1995), lung (Huang et al., 1992), oral/pharyngeal, esophageal (Galeone et al., 2005), and laryngeal (Bosetti et al., 2002) cancers.

7.2. Breast cancer

Evidence from some animal and epidemiological studies have suggested an increased risk of breast cancer associated with high intake of meat (De Stefani et al., 1997; Zheng et al., 1998; Sinha et al., 2000; Dai et al., 2002). In addition, the studies revealed the breast cancer is caused due to high intake of plant seed cooking oils (D'Avanzo et al., 1991; Favero et al., 1998; Zock et al., 1998). It has been reported that RCO not only produces fumes containing mutagenic compounds (i.e. benzene, acrolein, 1,3-butadiene, and formaldehyde), but also produces non-volatile hazardous compounds (hydroperoxides, *trans*-fatty acids, and aldehydes) (Grandgirard et al., 1984, Goburdhun et al., 2001). Both these hydroperoxides and aldehydes are endogenous reactive metabolites and possess mutagenic and carcinogenic properties (Gupta et al., 1999). Other epidemiological studies have also reported that a positive correlation between the intake of oil containing linoleic and linolenic acid and breast cancer risk (Klein et al., 2000; Pala et al., 2001). In Western countries, hydrogenated oils have been generally used for home cooking and food formulation and food processing in food industry have *trans*- fatty acids. These *trans*- fatty acids could be a high-risk factor for breast cancer (Kohlmeier et al., 1997).

7.3. Colorectal cancer

Normally, heterocyclic amines (HCAs) have been generated during the frying of protein rich food including meat, eggs and fish and HCAs have been proved as bacterial mutagens and animal carcinogens (Pfau and Marquardt, 2001). In an experimental animal study, these amines cause cancer especially in the organs such as breast, colorectal, stomach and pancreas (Galeone et al., 2007). An American case–control study also further reported that a positive relationship between pan-fried red meat intake and colon cancer risk (Butler et al., 2003), and other epidemiological studies also investigated a direct relationship with colorectal adenomas and cancer (Sinha et al., 2001; Navarro et al., 2004). In a cohort study on Swedish women, including 741 cases of colorectal cancer, there was a connection between the quantities of acrylamide intake and colorectal cancer (Mucci et al., 2006).

7.4. Prostate cancer

In a population-based study of 1096 controls, 717 localized and 1140 advanced cases, it was observed an increased risk of prostate cancer (PCa) relation with the intake of pan-fried meat (OR = 1.4; 95% CI, 1.0–1.8) adjusted for age, BMI, total intake of calorie, and family history (Joshi et al., 2012). In addition, the study had further reported the more relative risks of PCa connected with high intake of fish cooked with high-temperature cooking methods (Joshi et al., 2012). The carcinogen, acrylamide, is produced in an enormous quantity during deep-frying, especially carbohydrate-rich foods such as potatoes (Tareke et al., 2002). The positive correlation between acrylamide and PCa risk have been reported in two case-control studies and four cohort studies (Lipworth et al., 2012).

Normally, foods cooked with high temperature produces high levels of advanced glycation end products (AGEs) (Uribarri et al., 2010). For instance, a chicken breast deep-fried for 20 min generated nine times more quantities of AGEs as a chicken breast boiled for 60 min (Uribarri et al., 2010). These AGEs have been linked to increased oxidative stress and proinflammatory effects (Uribarri et al., 2007). These inflammatory effects may also play a vital role in PCa (De Marzo et al., 2007), and further *in vitro* studies have also suggested that the interactions between AGEs and the receptor of AGE could be a driver in PCa progression (Elangovan et al., 2012). Furthermore, the study associated with fast food restaurants and cooking methods, where the French fries prepared by commercial vegetable oils such as sunflower seed, canola, soybean, cottonseed, and palm oil (Jahren and Schubert, 2010). These oils are normally containing a high amount of omega-6 fatty acids, which have also been reported to induce proliferation of human prostate tumor (Hughes-Fulford et al., 2006). In animal study, the intake of omega-6-rich diets resulted in prostate tumor growth and development (Kelavkar et al., 2009). In human-based studies reported a higher risk of PCa associated with high intake of omega-6 fatty acids (Neuhouser et al., 2007).

8. Public awareness and legislation

An adequate quantity of oil is regularly required for deep-frying of the food materials. Therefore the person may regularly keep the used frying oil for future use. This practice usually maintains at household kitchens as well as various small scaled industrial sectors. Reusing this

frying oil is thought to limit the cost of food preparation without contemplating the potential toxic effects on human health. Despite the fact that about 70% of populations in Kuala Lumpur, Malaysia realize that the quality of cooking oil does not stay the same after deep-frying (Azman et al., 2012), reusing frying oil is still generally practiced in the population in Kuala Lumpur.

Public awareness with respect to the toxic of using RCO is still not satisfactory in developing and under-developed nations. About 60% of people have conceded utilizing still the same part of RCO (Phiri et al., 2006; Azman et al., 2012; Abdullah et al., 2010). A chemical investigation of the oils demonstrated the presence of FFA is almost thrice in the ranges of 0.84–1.4112 compared with the fresh oil (0.42). The peroxide value in RCO raise to 14.7–16.6 compared with 9.0 in the fresh oil (Phiri et al., 2006). In a Japanese survey, about 90% of the respondents had not been aware of food quality and safety issues of RCO (Phiri et al., 2006). Another study conducted in Japan found that restaurant frying oils were used at 180 °C for 3 h /day for five continuous days before disposing of those oils (Totani et al., 2006).

The impacts of heating process on the safety of cooking oils have drawn enormous attention from the researchers worldwide. During the recent 7th International Symposium on Deep-Fat Frying held in San Francisco, USA, scientists have reaffirmed that the best indices for evaluation of the used oils are total polar materials and polymeric TGL by using recognized methods (European Federation for the Science, Technology of Lipids, 2013). Peroxide value, FFA value, and anisidine value should not be used as regulatory indices when it comes to monitoring and comparing the degree of degradation of different frying oils. The cut-off point for rejection of reused frying oil has been proposed to be set at a content range of 20–27% for polar compounds (Paul and Mittal, 1997), which with the implementation of Hazard Analysis and Critical Control Point regulation has been employed in the national food laws in several European countries (Dobargarnes and Márquez-Ruiz, 1998).

Nonetheless, the index does not speak the careful bunch of products from lipid peroxidation as 25% of polar compounds in cooking oil relate to a considerably higher content of TGL oligomers (Bastida et al., 2002). Furthermore, some secondary oxidation products may have potential harmful to the human health. A study has found significant concentrations of toxic aldehydes present in the oil albeit the 25% limit for polar compounds is reached in the oil

(Guillén et al., 2012). These findings recommend that the limit may overlook and permits alternative arrangement of possible hazardous compounds. Since the products of lipid oxidation are nearly connected with CVD risk factors and cancers, the quality of the vegetable oil consumed daily unquestionably affects the cardiovascular system and progression of tumor/malignancies in various peripheral organs.

9. Conclusion and future directions

On the basis of the data discussed in the present review, consumption of diets containing RCO could be harmful and cause various cancers in peripheral organs. The nutritive and protective benefits of vegetable oils deteriorate when the oils are repeatedly exposed to extreme heat, air, and moisture, during food preparation, particularly in deep-fat frying. Through a complex series of reaction that occurs during deep-fat frying, various oxidation products including PAHs are formed, affecting the quality of oil physically and chemically. The data in this review suggest the deleterious effects of heated oils and their fumes produce various PAHs, they are mutagenic, genotoxic and carcinogenic agents. Studies report that RCO and its fumes may increase the risk of cancer via DNA mutations that initiate cancer. These progressions of cancer chemically induce by enzymes that react with DNA, leading to mutations. When the DNA sequence is altered in genes that regulate cell replication, cancer can result. However, the issue on re-using oil in food preparation has not been paid enough attention as the economic perspective of the food industry or the society is given more priority than health perspective of the consumers. Public education, awareness, and stringent laws are needed to contain the usage of thermally oxidized oil in food industry and households. Finally, though a substantial amount of *in vitro* and *in vivo* animal studies, the effects of heated oil in humans are still vaguely understood or contradictory. Since oil is an essential dietary component in daily meals, the mechanisms by which heated oil exerts its effects in humans merit further investigation in long-term, larger cohort studies to get ascertainable evidence as well as to increase awareness among the people.

Conflicts of Interest

The authors declare no conflict of interest.

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Author Contributions

K.S. and K.G. conceived, designed and wrote the review; B.X. critically read and improved the manuscript.

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Table 1: Physico-chemical changes during thermal oxidation of various cooking oils.

Vegetable oil	Temperature (°C)	Duration of heating	Physico-chemical changes	References
Canola oil	185 & 215	7 h/day	1. Decrease total polar compounds and anisidine value. 2. Increase vitamin E degradation	Aladedunye and Przybylski, 2009
Coconut, safflower, canola & olive oil	180, 210, 240, 270	6 h	Formation of acrolein increased with temperature.	Katragadda et al., 2010
Olive oil	180	1.5 – 25 h	1. Decrease the quantity of hydroxytyrosol& tyrosol like substances. 2. Degradation of vitamin E and glyceridic fractions. 3. Losses in polyphenols.	Brenes et al., 2002
	180	30–180 min	Decrease concentration of hydroxytyrosol, elenolic acid, decarboxymethyl oleuropein aglycon, and oleuropein aglycon	Carrasco-Pancorbo et al., 2007
Olive, corn, soybean oils	180	30, 60, 90 min	Increase peroxide value, *p*-anisidine value, FFA	Naz et al., 2005
Palm oil and soybean oil	180	Heated once & 5 times (10 mins)	Decrease vitamin E content and various isomers of vitamin E	Adam et al., 2007
Palm oil	30–320	0–20 min	Increase MDA content, decrease carotenoid content	Oboh et al., 2014
Peanut oil	220	20 min	1. Increase acid, peroxide value, MDA content. 2. Decrease of total carotenoid content	Falade and Oboh, 2015
Sunflower oil	100	52 h	Decrease amount of linoleic acid	Sadoudi et al., 2014
Sunflower, grapeseed, soybean, corn & olive oil	180	50 h	Increase quantity of conjugated trienes and total polar components.	Marinova et al., 2012

Table 2: *In-vitro* and *in vivo* genotoxicity and mutagenicity effect of RCO

Model	Deep fried oil	Negative control	Investigation	Results	References
Wistar albino rats and Salmonella tester strain TA97, TA100	coconut oil and palm oil	mutagenic to strain TA100	TBARS, hydroperoxides, mutagenicity of urine and faeces, alkaline phosphatase, cell proliferative indices in the gastro-intestinal tract	Genotoxicity and mutagenicity effect	Hageman et al., 1991
Human lung carcinoma pulmonary type II-like epithelium cell (A-549 cell)	soybean oil, sunflower oil, and lard	trans-trans-2,4-decadienal, t-t-2,4-DDE; trans-trans-2,4-nonadienal, t-t-2,4-NDE; trans-2-decenal, t-2-DCA and trans-2-undecenal, t-2-UDA	GSH, GST, GSR and ROS assay	Genotoxicity and mutagenicity effect	Dung et al., 2006
Wistar albino rats and Salmonella tester strain TA97, TA100	coconut oil and palm oil	mutagenic to strain TA100	TBARS, mutagenicity of urine and faeces, cell proliferative indices in the gastro-intestinal tract	Genotoxicity and mutagenicity effect	Hageman et al., 1990
Wistar albino rats	soybean oil and coconut oil	-	fatty acid synthase, acetyl-CoA-carboxylase, glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and ATP citrate lyase, TGL, TBARS,	Genotoxicity and mutagenicity effect	Eder and Kirchgessner, 1998
Salmonella tester strain TA97, TA100	Peanut oil	trans-trans-2,4-decadienal, trans-trans-2,4-nonadienal, trans-2-decenal, trans-2-undecenal	smoke point, unsaturated fatty acids, fume formation, and assay of mutagenicity effect	mutagenicity effect	Wu et al., 2001
In vitro	Lard, soybean oil, peanut oil	polycyclic aromatic hydrocarbons, (benzo(a)pyrene, benz(a)anthracene, and dibenz(a,h)anthracene	Assay of mutagenicity effect	mutagenicity effect	Wu et al., 1998
Human and Salmonella tester strain TA97	Lard, soybean oil, peanut oil	dibenz[a,h]anthracene and benz[a]anthracene	Assay of mutagenicity effect	mutagenicity effect	Chiang et al., 1997
Human	Safflower, olive, coconut, mustard, and corn	enzo[a]pyrene, dibenz[a,h]anthracene, benzo[b]fluoranthene and benzo[a]anthracene	HPLC, GC-MS assay, Ames test, sister chromatid exchange, and SOS chromotest	Genotoxicity	Chiang et al., 1999b
Wistar albino rats	Coconut oil	diethylnitrosamine	SOD, CAT, GGT, GST	Genotoxicity and mutagenicity effect	Srivastava et al., 2010a
Wistar albino rats	Sunflower oil	polycyclic aromatic hydrocarbons	SOD, CAT, GGT, GST. ATP, ALP glucose-6-phosphatase	Genotoxicity and mutagenicity effect	Srivastava et al., 2010b
Wistar albino rats	Soybean oil	cooking oil fume	MTT reduction assay, type II pneumocytes were studied by modified alkaline single-cell gel using a electrophoresis assay (comet	DNA damage and genotoxicity effect	Zhang et al., 2002

			assay),		
Mice	Rapeseed oil, Peanut oil, and lard	cooking oil fume	Salmonella mutation assay, SV50 forward mutation assay, and sister chromatid exchange assay, as well as the micronucleus assay in mouse bone marrow	Mutagenicity effect	Qu et al., 1992
Salmonella typhimurium tester strains TA98 and TA104	Chinese rapeseed, refined Canola, soybean, and peanut oil	cooking oil fume	Salmonella mutation assay	Mutagenicity effect	Shields et al., 1995
Human	Peanut, soybean, and Canola oils	cooking oil fume	Determination of 1,3-butadiene, benzene, and a series of aldehydes, olefins, and saturated hydrocarbons	Genotoxicity effect	Pellizzari et al., 1995
Wistar albino rats, hamster, mice	Canola, soybean, and peanut oil	cooking oil fume	Salmonella mutagenesis (Ames test); forward mutagenesis of mouse lymphoma cells at the thymidine kinase locus; unscheduled DNA synthesis in rat hepatocytes; and clastogenicity in cultured Chinese hamster ovary cells	Genotoxicity effect	Williams et al., 1996
Salmonella typhimurium tester strains TA98 and TA104; Chinese hamster lung cells (CHL/IU	Canola, soybean, and peanut oil	cooking oil fume	Bacterial reverse mutation assay (Ames test), the chromosomal aberration assay in cultured Chinese hamster lung cells and a bone marrow micronucleus assay	Genotoxicity effect	Kasamatsu et al., 2005
Sprague-Dawley rats and ICR mice	Sesame seeds and oil	cooking oil fume	Bacterial reverse mutation assay (Ames test), the chromosomal aberration assay in cultured Chinese hamster lung cells and a bone marrow micronucleus assay	Genotoxicity effect	Hori et al., 2011
Sprague-Dawley rats and ICR mice	Licorice flavonoid oil	cooking oil fume	Bacterial reverse mutation assay (Ames test), the chromosomal aberration assay in cultured Chinese hamster lung cells and a bone marrow micronucleus assay	Genotoxicity effect	Nakagawa et al., 2008
Sprague-Dawley rats	Rapeseed oil	cooking oil fume	Rat liver microsomal S9 fraction	Genotoxicity effect	Topinka et al., 2012

Table 3: Impact of RCO on tumourigenic effect

Model	Deep fried oil	Negative control	Investigation	Results	References
Wistar albino rats	Mustard oil	Diethylnitrosamine	GST, GGT, liver weight	Tumourigenic effect	Shukla and Arora, 2003
Wistar albino rats	Mustard oil	Diethylnitrosamine	GST, GGT, liver weight alkaline phosphatase, adenosine triphosphatase, glucose-6-phosphatase	Tumourigenic effect	Shukla and Arora, 2003
Wistar albino rats	Mustard oil	Diethylnitrosamine	GST, GGT, liver weight ALP, adenosine triphosphatase, glucose-6-phosphatase	Tumourigenic effect	Kim et al., 1994; Shukla et al., 2004
Rabbit	soybean, and peanut oil	Heated lipiodol	Vascular endothelial growth factor receptor (VEGFR) and vascular endothelial growth factor (VEGF) expression levels, Proliferating cell nuclear antigen (PCNA) expression	Enhance tumor angiogenesis	Cao et al., 2013
Rabbit	Canola oil	Ferucarbotran and lipiodol	Apoptosis assay by TUNEL staining	Enhance tumor angiogenesis	Takamatsu et al., 2008
Rabbit	Canola, soybean, and peanut oil	Heated doxorubicin-lipiodol	serum AST levels	Enhance tumor angiogenesis	Cao et al., 2010
Human bronchial epithelial cells (BEAS-2B cells	Peanut oil	Trans, trans-2,4-decadienal	ROS production, GSH/GSSG ratio, cell proliferation, and expression of TNFalpha and IL-1beta	Tumourigenic and genotoxicity effect	Chang et al., 2005
Human bronchial epithelial cells (BEAS-2B cells	Soybean and peanut oil	Trans, trans-2,4-decadienal	Vitamin C and N-acetylcysteine, downstream targets of p27, including CDK4, cyclin D1 and phosphorylated-Rb proteins	Tumourigenic and genotoxicity effect	Chang and Lin, 2008
Human bronchial epithelial cells (BEAS-2B cells	Canola oil	Trans, trans-2,4-decadienal	endonuclease III/formamidopyrimidine-DNA glycosylase, nucleotide excision repair enzymes	Tumourigenic and genotoxicity effect	Young et al., 2010
Human bronchial epithelial cells (BEAS-2B cells	Canola, soybean, and peanut oil	Trans, trans-2,4-decadienal	Oxidative stress markers	Tumourigenic and genotoxicity effect	Lin et al., 2008

Table 4: Impact of RCO on various cancers

Model	Deep fried oil	Negative control	Investigation	Results	References
Human lung carcinoma pulmonary type II-like epithelium cell (A-549 cell)	Soybean oil, sunflower seed oil, and lard	Trans-trans-2,4-decadienal, t-t-2,4-DDE; trans-trans-2,4-nonadienal, t-t-2,4-NDE; trans-2-decenal, t-2-DCA and trans-2-undecenal, t-2-UDA	GSH, GST, GSR and ROS assay	Women exposed to emitted fumes from cooking oil cause at higher risk of lung cancer	Dung et al., 2006
Human lung carcinoma pulmonary type II-like epithelium cell (A-549 cell)	Soybean oil and sunflower oil	Trans-trans-2,4-decadienal, t-t-2,4-DDE	GSH, GST, GSR, ROS	Fumes from cooking oil cause at higher risk of lung cancer	Wu and Yen, 2004
human hepatoma HepG2 cells	Olive oil	Tertbutyl hydroperoxide	GSH, GST, GPx, MDA	Liver cancer	Alía et al., 2006; Goya et al., 2007
Human	Sunflower oil, lord oil	Salmonella tester strain TA97	HPLC, GC-MS, and assay of 2-naphthylamine and 4-aminobiphenyl	Bladder cancer	Chiang et al., 1999a
Human	Vegetable oils	Cooking oil fumes	Analysis of DNA damage	Lung cancer	Lee and Gany, 2013
Human	Rapeseed oil	Cooking oil fumes	Exposure to indoor air pollutants from Chinese-style cooking was ascertained through in-person interviews	Lung cancer	Zhong et al., 1999a
Human	Vegetable oils	Cooking oil fumes	Analysis of DNA damage	lung cancer	Liu et al., 1993
Mouse colon carcinoma (MC38) cells and Hodgkin's lymphoma (L428) cells.	Vegetable oils	Cooking oil	Analysis of NF-κB pathway	Colon cancer	Agbaria et al., 2015
Human obese	Sunflower seed oil and virgin olive oil	Dimethylsiloxane	Assay of omega-3 and omega-6 EFAs	Vascular cancer	Orozco-Solano et al., 2013
Human lung adenocarcinoma CL-3 cells	Soybean oil	Cooking oil fumes and H_2O_2	Assay human 8-oxoguanine DNA glycosylase 1	Lung cancer	Cherng et al., 2002
Human lung adenocarcinoma CL-3 cells	Rapeseed oil	Cooking oil fumes	Assay of TGF beta1, TGF beta2, IL-6, IL-8, and IFN-gamma gene expressions with the RT-PCR method;	Lung cancer	Tung et al., 2001

			intracellular peroxide formation by dichlorofluorescein method		
Human lung adenocarcinoma A549 cells	Rapeseed oil	Benzo[a]pyrene (BaP) and 2,4-decadienal	Assay of IAP2 and phosphorylated Akt proteins, Flow cytometry and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) analysis	Lung cancer	Hung et al., 2007
Wistar albino rats	Soybean oil	Cooking oil fume	Assay of MDA, N-acetylcysteine, GSH	Lung cancer	Pu et al., 2002
Human	Vegetable oils	Cooking oil fume	Epidemiological study	Lung cancer	Zhong et al., 1999b
Human	Vegetable oils	Cooking oil fume	Epidemiological study	Lung cancer	Purcaro et al., 2006
Salmonella TA98 and mouse	Rapeseed oil	Cooking oil fume	Ames test, SCE/V79 in vitro and mice micronucleus in vivo test	Lung cancer	Chen et al., 1992
Human	Vegetable oils	Cooking oil fume	Pap smear screening and biopsy examination, community-based case-control study	Cervical cancer	Velema et al., 2002; Lee et al., 2010
Human	Vegetable oils	Cooking oil fume	Histological analysis	Lung cancer	Ko et al., 1997; 2000
Human	Vegetable oils	Cooking oil fume	Histological analysis	Lung cancer	Seow et al., 2000
Wistar albino rats	Mustard oil	Diethylnitrosamine	GST, GGT, liver weight ALP, adenosine triphosphatase, glucose-6-phosphatase	Lung cancer	Kim et al., 1994; Shukla et al., 2004
Human	Vegetable oils	French fries, fried chicken, fried fish, doughnuts and snack chips	Structured questionnaire, BMI,	Prostate cancer	Stott-Miller et al., 2013
Human	Vegetable oils	French fries, fried chicken, fried fish,	Structured questionnaire, BMI,	Prostate cancer	Pawlega et al., 1996
Human	Vegetable oils	French fries, fried chicken, fried fish,	Structured questionnaire, BMI,	Prostate cancer	Li et al., 2014
Human	Olive oil	Fried foods	Structured questionnaire, BMI,	Colorectal cancer	Galeone et al., 2007
Human	Olive oil	Fried fishes	Structured questionnaire	Prostate cancer	Joshi et al., 2012
Human	Vegetable oils	Fried bread, rice, and red meat and deep fried vegetables	Structured questionnaire-gender, age, body mass index, years of education, diabetes and alcohol history, smoking status, and opium use	Pancreatic cancer	Ghorbani et al., 2015
Human	Soybean oil	Fried fishes	Structured questionnaire	Breast cancer	Dai et al., 2002
Human	Vegetable oils	Fried foods	Structured questionnaire	Gastric cancer	Somi et al., 2015
Human	Vegetable oils	potato crisps, chips (deep-	Structured questionnaire	Gastric cancer	Konings et al., 2003; Svensson

		fried), cocktail snacks, and gingerbread			et al., 2003; Mojska et al., 2010
Human	Vegetable oils	Fried foods	Structured questionnaire	Pharyngeal cancer	Zheng et al., 1992
Human	Vegetable oils	Fried foods	Structured questionnaire	Pharyngeal cancer	Ji et al., 1995
Human	Vegetable oils	Tofu, deep-fried tofu, raw fish, and tempura,	Structured questionnaire	Pancreas cancer	Ohba et al., 1996
Human	Vegetable oils	benzo(a)pyrene-containing barbecued, smoked or deep-fried meats	Dietary intake exposure assessment, and intra-individual variance	Lung cancer	Cai et al., 2012; Zhang et al., 2012; Nie et al., 2014; Duan et al., 2016
Human	Vegetable oils	Fried foods	Structured questionnaire and hematological profile	leukemia	Liu et al., 2015
Human	Vegetable oils	Fried foods	Structured questionnaire and hematological profile	Breast cancer	Kojima et al., 2017
Human	Vegetable oils	Fried foods	Structured questionnaire	Stomach cancer	Pham et al., 2010
Human	Vegetable oils	Fried foods	Structured questionnaire	Breast cancer	Cottet et al., 2009; Catsburg et al., 2015
Human	Vegetable oils	Deep fried vegetables	Structured questionnaire	Pancreas cancer	Ghorbani et al., 2015
Human	Vegetable oils	Deep fried foods	Structured questionnaire	endometrial adenocarcinoma	Takayama et al., 2013
Human	Vegetable oils	Deep fried foods	Structured questionnaire	Breast cancer	Datta and Biswas, 2009
Human	Vegetable oils	Deep fried foods	Structured questionnaire	Breast cancer	Hanf and Gonder, 2005
Human	Vegetable oils	Deep fried meats	Structured questionnaire	colon and rectal cancer	Lüchtenborg et al., 2005

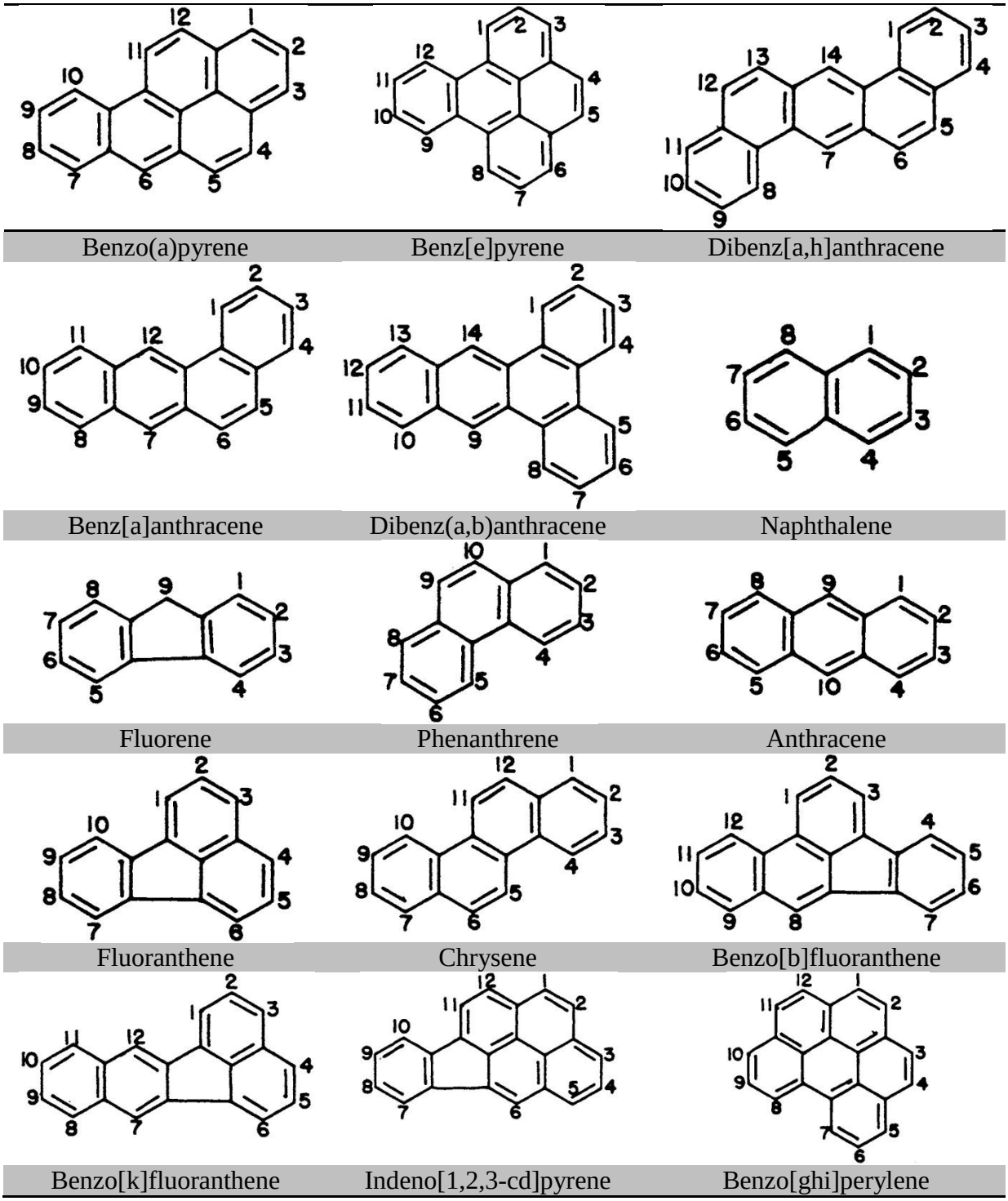

Figure 1: List of PAHs in cooking oil fumes (Li et al., 1992, 2003; Chen et al., 2012; Yao et al., 2015)

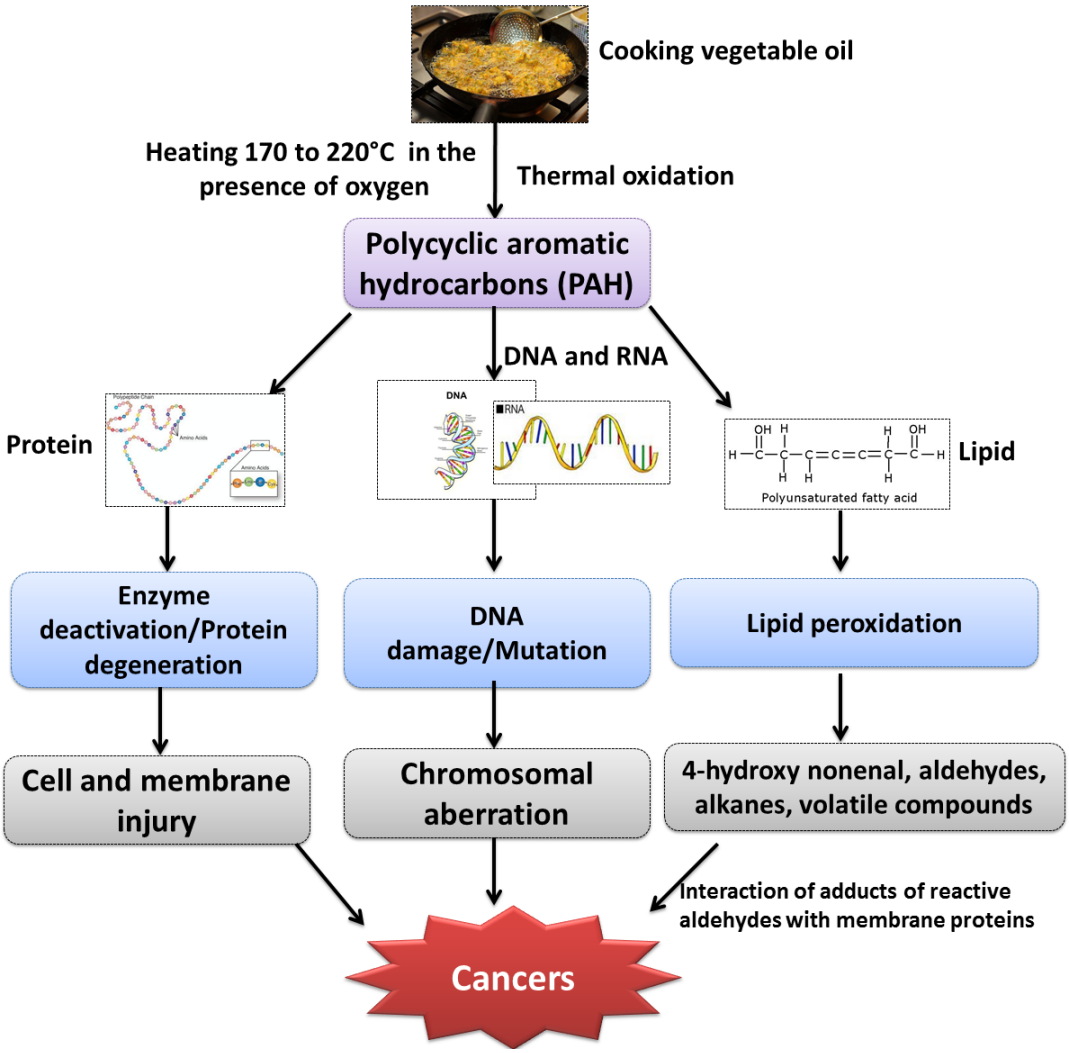

Figure 2: Repeatedly heated cooking oil emits PAHs and subsequent causes of cancer