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REVIEW

Shellfish consumption and health: A comprehensive review of human studies and recommendations for enhanced public policy

Lei Xu, Jing Cai, Tianlin Gao, and Aiguo Ma

Institute of Nutrition and Health, School of Public Health, Qingdao University, Qngdao, China

ABSTRACT
Shellfish, including various species of mollusks (e.g., clams, oysters, and mussels) and crustaceans (e.g., shrimp and crab), have been a cornerstone of healthy dietary recommendations. However, beyond providing basic nutrition needs, their health-promoting effects have been suggested to include inflammation reduction and prevention of various chronic non-communicable diseases. Currently, studies on the association between shellfish consumption and health outcomes have reported conflicting results. The present comprehensive review summarized the latest studies on shellfish consumption and synthesized the available evidence on the potential health benefits or risks of shellfish consumption. The findings demonstrated that shellfish consumption may increase the risk of hyperuricemia and gout but may not increase the risk of type 2 diabetes, cardiovascular diseases, and thyroid cancer. Adequate evidence is lacking on the association between shellfish consumption and the risk of colorectal cancer, pancreatic cancer, oral cancer, endometriosis, hip fracture, cognitive function, wheeze, eczema and food allergy. Raw shellfish consumption may cause gastroenteritis and other diseases infected by bacteria or viruses. This review thus provides consumers and other relevant stakeholders with the latest evidence-based information on the potential benefits and risks of shellfish consumption.

KEYWORDS
Seafood; shellfish; shrimp; chronic diseases; health; review

Introduction

Oceans are deeply intertwined with the health and well-being of human societies. Leading international and national bodies have conducted many studies on oceans and human health as a priority (Schuldt et al. 2016). Establishing a definitive evidence-based link between the oceans and public health is an ongoing research effort. Chronic noncommunicable diseases, such as type 2 diabetes, cardiovascular diseases, and cancers, have been the leading causes of morbidity and mortality globally (World Health Organization 2018), representing a considerable public health burden. Outbreaks and sporadic cases of foodborne diseases occur regularly (Kirk et al. 2015). Shellfish, including various species of mollusks (e.g., clams, oysters, and mussels) and crustaceans (e.g., shrimp, crab), are a critical component of aquatic products (Lopata et al. 2010) and is consumed globally because of its nutritional benefits and flavor. **Table 1** outlines the classification of the main edible shellfish.

Current gaps in shellfish consumption

In 2018, there were 17.7 million tons of edible mollusks, 9.4 million tons of crustaceans in aquaculture worldwide (Food and Agriculture Organization 2020). In the United States, the average seafood intake was approximately 1.3 servings weekly in 2012, a modest increase from 1.1 servings weekly in 1999 but still well below the dietary guidelines recommendations (Rehm et al. 2016). In 2018, shrimp consumption in the United States was approximately 2.09 kg/person/year (National Fisheries Institute 2017). In Europe, mollusk consumption between consumers and nonconsumers may differ by more than 70 times, with the largest consumer being Belgium (elderly) at 72.1 g per capita per day. France (teenagers) and Ireland (adults) have the lowest per capita mollusk consumption (only 11.8 g per day) (European Food Safety Authority 2011). In China, the aquatic products consumed are mainly fish and shrimp, with the average daily intake for adults being 28.6 g; of that, 78.7% comes from fish, and shrimp, crabs, and mollusks account for 6.9%, 5.1%, and 9.3%, respectively (Su et al. 2018). The mean seafood consumption of the cluster (including Japan, Korea, Madagascar, and the Philippines) was 69.0 g/person/day, approximately 25% of which comprises mollusks, crustaceans, and cephalopods. South-East Asia has a mean seafood consumption of 45.0 g/person/day, with 40% being contributed by mollusks, crustaceans, and cephalopods (Sioen et al. 2009). In general, due to cultural differences and the availability of seafood, seafood consumption (amount and species consumed) differs considerably across the globe.

Contribution to nutrient intake

Considerable evidence exists on the health benefits of seafood consumption. Shellfish are a major source of protein for many coastal and island populations. In South Korea,

CONTACT Aiguo Ma magfood@qdu.edu.cn Institute of Nutrition and Health, School of Public Health, Qingdao University, Qingdao 266021, China

Table 1. Classification of main edible shellfish.

Common reference	Phyla	Class	Common Name
Shellfish (invertebrates)	Mollusca	Bivalvia	Mussel oyster clam scallop cockle
		Cephalopoda	Squid octopus cuttlefish
		Gastropoda	Abalone snail limpet
	Arthropoda	Malacostraca	Shrimp prawn lobster crayfish krill crab

>10% of the daily protein intake is derived from shellfish (Oehlenschläger 2012). Shellfish protein is, in general, of good quality (Pak et al. 1985). Humans consume taurine largely through seafood, especially some marine invertebrates, which contain high amounts of taurine compared with meat (Tsuji and Yano 1984). Oyster meat is rich in taurine (more than 1 mg/100 g). Shellfish are also an essential source of omega-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Passi et al. 2002; Mahaffey 2004). Moreover, different shellfish are rich in different minerals (e.g., iron, zinc, selenium, and iodine), vitamins (e.g., vitamin D). Shellfish vary widely in their nutrient content but in general are valuable additions to the diet (King et al. 1990).

Risks of shellfish consumption

Increasing shellfish consumption to achieve adequate nutrient intake can also increase the contaminant intake, which may be sufficiently high to be of toxicological concern. Pollution of the oceans is widespread and worsening, and pollutants include toxic metals (e.g., methyl mercury), plastic waste (e.g., microplastics), and manufactured chemicals (e.g., polychlorinated and polybrominated biphenyls) (Abdallah 2013; Smith et al. 2018). Shellfish-associated infections are caused by various bacteria (e.g., *Vibrio parahaemolyticus*, *Salmonella*, and *Shigella*), viruses (e.g., norovirus and hepatitis A virus), and parasites (e.g., helminths and protozoa) (Iwamoto et al. 2010). This diverse group of pathogens results in a wide variety of clinical syndromes. Viruses are the leading cause of acute gastroenteritis. Most cases of acute gastroenteritis are self-limiting, but some patients with more serious infections resulting from invasive bacterial and parasitic organisms may present with life-threatening dehydration and shock (Lai et al. 2016; Reeve et al. 1989; Wilson et al. 1981; Hamano et al. 2005). Shellfish-associated acute gastroenteritis is most commonly caused by the consumption of shrimps, crabs, lobsters, clams, and oysters.

Notably, filter-feeding shellfish such as oysters and mussels ingest toxic algae, known as harmful algal blooms, and accumulate algal toxins, causing acute poisoning syndromes in shellfish eaters, such as paralytic, neurotoxic, amnesic, diarrhetic, and other gastrointestinal poisoning (Vilariño et al. 2018; Morabito et al. 2018). Paralytic shellfish poisoning is caused by saxitoxins. These potent toxins inhibit the generation of action potentials in the membranes of neurons and muscle cells (Duran-Riveroll and Cembella 2017), and typically begin with tingling sensations or numbness of the mouth, neck, fingers, and toes, and progress to weakness, limb incoordination, and respiratory difficulty (Vilariño et al. 2018; Landrigan et al. 2020). Amnesic shellfish poisoning is caused by domoic acid produced by planktonic diatoms. It targets glutamate receptors in the central nervous system (Bates et al. 2018; Iverson and Truelove 1994). After initial gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, and abdominal cramps), affected individuals develop neurological symptoms (e.g., confusion, short-term memory loss, and coma) (Teitelbaum et al. 1990). Diarrhetic shellfish poisoning is associated with exposure to okadaic acid and dinophysis toxins and manifests as diarrhea, nausea, vomiting, and abdominal pain (Morabito et al. 2018). Neurotoxic shellfish poisoning is caused by brevetoxins, neurotoxins that target voltage-gated sodium channels and cause depolarization of neuronal, muscular, and cardiac cells (Dechraoui et al. 1999). Neurotoxic shellfish poisoning causes gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea), and neurologic symptoms (e.g., paralysis, and coma) (Watkins et al. 2008). Ciguatera fish poisoning is caused by the consumption of fish and shellfish that have accumulated ciguatoxins in their tissues (Darius et al. 2017; Clausing et al. 2018). Ciguatoxins are neurotoxins that target voltage-gated sodium channels and symptoms include gastrointestinal distress that may occur before or simultaneously with neurological symptoms, and cardiovascular symptoms (Friedman et al. 2017). In brief, each toxin syndrome has a different lethal dose, onset and duration time, and a range of symptoms.

The balance of the ingested nutrients and contaminants depends on the quantity and species of the seafood consumed. Several experimental and epidemiological studies have concluded that the benefits of seafood intake exceed the potential risks even for vulnerable consumer groups (Jacobs et al. 2018). Although nutritional authorities recommend increasing seafood consumption, awareness or concerns about shellfish could lead consumers to reduce their shellfish consumption (Jacobs et al. 2018; Domingo 2016).

Currently, data from epidemiological studies on the association of shellfish consumption with health outcomes are controversial. A comprehensive evaluation of this associated is vital to reduce consumers' health risks and support their nutritional health. Therefore, we conducted this comprehensive review of human studies to evaluate the association between shellfish consumption and health outcomes. Our findings may help policymakers to prepare guidelines for improving shellfish consumption.

Methods

Literature search and selection criteria

A systematic literature search was performed in the PubMed databases until July 31, 2020 using the search strategy. The search keywords were "seafood, shellfish, mussel, oyster, clam, scallop, cockle, squid, octopus, cuttlefish, abalone, snail, limpet, shrimp, prawn, lobster, crayfish, krill, crab". We included all human studies and meta-analyses of human studies. One investigator performed the primary title and abstract screening. The full texts of all potentially eligible articles were retrieved, and consensus between two investigators determined the final eligibility of each manuscript. The references of selected articles were also hand-searched to identify other pertinent documents.

Data extraction

Two investigators extracted the following information for each article: (1) the first Author's name, (2) year of publication, (3) country in which the study was conducted, (4) the sex, age of participants, (5) exposure (the types of shellfish they measured), (6) outcome variable (e.g., type 2 diabetes), (7) the most-adjusted, study-specific estimates for the health outcome (e.g., relative risk (RR), odds ratio (OR), hazard ratio (HR), or incident risk ratio), along with the 95% confidence interval (CI). For articles that had separate results for male and female, we considered them as two independent studies.

Eligible studies

A total of 126,957 publications could be identified after elimination of duplicate documents. Ultimately, 39 publications were identified in the analysis for the association between shellfish consumption and chronic non-communicable diseases. Type 2 diabetes, hyperuricemia and gout, thyroid cancer were the most frequently assessed disease outcome, with other disease states such as endometriosis, cancer other than thyroid cancer, among others, being less common. This review was focused on the major global causes of morbidity: type 2 diabetes, hyperuricemia and gout, cardiovascular diseases, cancers, and other important health topics. The description of studies investigating the association between shellfish consumption and chronic non-communicable diseases are shown in Table 2.

Effects of shellfish consumption on health outcomes

Type 2 diabetes

Type 2 diabetes is a chronic metabolic disease associated with decreased insulin sensitivity. Approximately 700 million people worldwide are estimated to have type 2 diabetes by 2045 (International Federation Diabetes 2019). In the Western Pacific region, 153 million adults have diabetes, which is substantially more than China or India (American Diabetes Association 2012). In Asia, type 2 diabetes tends to develop at a younger age and in those with a lower body mass index than in Europe and North America (Mambiya et al. 2019). Two prospective cohort studies (Patel et al. 2009; Wallin et al. 2017) found that shellfish consumption was positively associated with the risk of type 2 diabetes. One prospective cohort study (Nanri et al. 2011) indicated a negative association between shellfish consumption and type 2 diabetes, and three cohort studies (Villegas et al. 2011; van Woudenbergh et al. 2009; Kaushik et al. 2009), one case-cohort study (Patel et al. 2012), and one cross-sectional study (Sahay et al. 2015) revealed no apparent association. A meta-analysis (Zhang et al. 2013) focused on fish and marine n-3 LC-PUFA consumption and incidence of type 2 diabetes. The shellfish data as a stratified sample involved only three articles and revealed no apparent association. A meta-analysis (Namazi et al. 2019) of five articles revealed that the risk of type 2 diabetes in patients with the highest consumption of seafood other than fish (shellfish) was not significantly different from those with the lowest intake (RR = 0.95; 95% CI, 0.83–1.10). Notably, in this meta-analysis, country, sex, and weight were sources of heterogeneity.

Insulin resistance leads to postprandial hyperglycemia, elevated free fatty acid levels, hyperinsulinemia, and pancreatic β-cell dysfunction, resulting in obesity and type 2 diabetes (Lalia and Lanza 2016). A potential mechanism underlying the protective effect of shellfish consumption against insulin resistance and type 2 diabetes may be related to n-3 LC-PUFA. One study indicated that high n-3 LC-PUFA consumption increases insulin sensitivity, may reduce free fatty acid mobilization by catecholamines, and reduces inflammatory markers in older people (Tsitouras et al. 2008). Similarly, another study demonstrated that improved insulin sensitivity because of supplementation with dietary n-3 LC-PUFA in patients with type 2 diabetes (Popp-Snijders et al. 1987). By contrast, several studies reported no effect of n-3 LC-PUFA on insulin sensitivity in patients with type 2 diabetes (Griffin et al. 2006; Kabir et al. 2007). Thus, n-3 LC-PUFA are protective against insulin resistance but not in all people and not at low daily doses. Several meta-analyses have also concluded that n-3 LC-PUFA have a protective effect on Asians and an increased risk in Western populations, but the heterogeneity of studies included was low in Asian populations and high in Western populations, which may explain the result in Westerners (Wu et al. 2012; Chen et al. 2017). In addition, consumption of high-temperature-cooked (e.g., fried) food induces the formation of advanced glycation end products, leading to insulin resistance and the formation of mutagenic compounds (Mark et al. 2014; Felton et al. 1997). Few epidemiological studies have taken preparation methods into consideration.

Hyperuricemia and gout

Persistent hyperuricemia can lead to the formation of uric acid crystals and precipitate the onset of gout. Five studies have analyzed the association between shellfish consumption and hyperuricemia or gout: two cross-sectional studies, one case–control study, and two cohort studies (Villegas et al. 2012; Chang 2011; Wang et al. 2013; Choi et al. 2004; Miao et al. 2008). The production and catabolism of purines are relatively constant. The kidneys eliminate approximately two-thirds and the gastrointestinal tract eliminates one-third of the uric acid load. Almost all uric acid is filtered from the glomeruli, while postglomerular reabsorption and

Table 2. Description of studies investigating the association between shellfish consumption and chronic non-communicable diseases.

First Author (year)	Design	Country	Sample	Age (Sex)	Exposure	Exposure category (lowest versus highest)	Outcome	Adjusted RR/OR/HR (95%CI)
Patel, P. S. (2009)	cohort study	England	21,984	40–79 (both)	shellfish	≥1/wk vs. ＜1/wk	type 2 diabetes	1.35 (1.01–1.79)
Wallin, A. (2017)	cohort study	Sweden	35,583	45–79 (M)	shellfish	≥1/wk vs. 0/wk	type 2 diabetes	1.19 (1.04–1.35)
Nanri, A. (2011)	cohort study	Japan	22,921	45–75 (M)	shellfish (e.g., shrimp, clam)	Median intake: 31.3 g/d vs. 4.7 g/d	type 2 diabetes	0.89 (0.68–1.17)
			29,759	45–75 (F)	shellfish (e.g., shrimp, clam)	Median intake: 28.2 g/d vs. 4.0 g/d	type 2 diabetes	0.93 (0.67–1.30)
Villegas, R. (2011)	cohort study	China	51,936	40–74 (M)	shellfish	Median intake: 24.3 g/d vs. 1.6 g/d	type 2 diabetes	0.82 (0.65–1.02)
			64,193	40–70 (F)	shellfish	Median intake: 23.5 g/d vs. 1.4 g/d	type 2 diabetes	0.86 (0.76–0.99)
van Woudenbergh, G. J. (2009)	cohort study	Netherlands	4,472	≥55 (M)	shellfish	>0g/d vs. 0 g/d	type 2 diabetes	1.04 (0.61–1.77)
Kaushik, M. (2009)	cohort study	the United States	195,204	39–72 (both)	shrimp, scallops, and lobster	≥1/mo vs. ＜1/mo	type 2 diabetes	1.06 (0.97–1.13)
Patel, P. S. (2012)	cohort study	8 European countries	24,813	>40 (both)	shellfish	30.3g/wk vs.0g	type 2 diabetes	1.05 (0.92–1.20)
Sahay, R. D. (2015)	cross-sectional study	Croatia	1,377	21–94 (M)	shellfish	Intake: 0 vs. >9.6 g/1000 kcal/d	type 2 diabetes	1.16 (0.76–1.79)
Zhang, M. (2013)	Meta-analysis	/	/	/	shellfish	highest vs. lowest	type 2 diabetes	1.03 (0.83–1.29)
Namazi, N. (2019)	Meta-analysis	/	/	/	seafood other than fish (shellfish)	highest vs. lowest	type 2 diabetes	0.95 (0.83–1.10)
Villegas, R. (2010)	cross-sectional study	China	3,978	40–74 (M)	shellfish	Median intake: 0.8 g/d vs. 32.8 g/d	hyperuricemia	1.14 (0.87–1.49)
Chang, W. C. (2011)	cross-sectional study	China	752	≥65 (M)	Crustaceans; mollusks	Crustaceans: ≥1 time/mo; Mollusks: ≥1 time/wk	untreated hyperuricemia; treated hyperuricemia	1.27 (1.03–1.56); 1.70 (1.14–2.54)
Wang, Y. (2012)	cohort study	China	659	18–93 (both)	shrimp, shell	Median intake: 50 g/d (shrimp), 100 g/d (shell)	gout	$P = 0.038$ $P < 0.001$
Choi, H. K. (2004)	cohort study	the United States	47,150	40–75 (both)	shrimp, lobster, or scallops	<1 serving/mo vs. 1-3 serving/mo; ≥1 serving/wk	gout	1.23 (1.04–1.45) 1.30 (0.99–1.70)
Miao, Z. (2008)	case-control study	China	5,003	20–80 (both)	shrimp, mollusks	Hyperuricemia: 37.78 ± 85.57 g/d control: 20.29 ± 36.29g/d	hyperuricemia	1.34 (1.20–1.27)
Matheson, E. M. (2009)	cohort study	the United States	13,355	45–64 (both)	shellfish	Almost never vs. ≥1 time/wk	coronary heart disease	0.98 (0.82–1.18)
Myint, P. K. (2006)	cohort study	Europe	24,312	40–79 (both)	shellfish	consumers vs. non-consumers	stroke	0.99 (0.73– 1.37) 1.08 (0.71–1.42)
Yuan, J. M. (2001)	cohort study	China	18,244	45–64 (M)	shellfish	<10g/wk vs. ≥100 g/wk	acute myocardial infarction; other ischemic heart disease; stroke	0.40 (0.82–1.18); 0.58 (0.17–1.02); 1.02 (0.69–1.51)
Durga, A. V. (2019)	case-control study	India	case:150 control:150	19–80 (both)	shrimp, crab	Median intake: case: 29 g/wk control: 45 g/wk	stroke	0.55 (0.32–0.95)
Yamamoto, A. (2018)	cohort study	the United States	81,908	26–42 (F)	shellfish	1 serving/mo vs. ≥2 servings/wk	endometriosis	1.04 (0.79–1.38)
Fan, F. (2013)	case-control study	China	case:581 control:581	55–80 (both)	mollusca and shellfish	Mean intake (M/F): 0.27/0.08g/d vs. 16.04/11.15g/d	hip fracture	0.55 (0.34–0.88)

Grattan, L. M. (2016)	cohort study	the United States	513	average age:36.3 (both)	razor clams	non-consumers vs. (high consumers (greater than 15 razor clams/mo)	cognitive function	$P \leq 0.05$
Liu, Z. T. (2014)	Meta-analysis	/	/	/	shellfish	highest vs. lowest	thyroid cancer	0.88 (0.72–1.08)
Cao, L. Z. (2017)	Meta-analysis	/	/	/	shellfish	highest vs. lowest	thyroid cancer	0.70 (0.52–0.96)
Preston-Martin, S. (1993)	case-control study	China	case:207 control:207	18–54 (F)	shellfish	never or infrequently vs. daily	thyroid cancer	1.3 (0.6–2.6)
Wingren, G. (1993)	case-control study	Sweden	case:104 control:387	20-60 (F)	shellfish	≥1 time/wk vs. never or infrequently	papillary thyroid cancer	2.5 (1.0–6.6)
Hallquist, A. (1994)	case-control study	Sweden	case:180 control:360	≥20 (both)	shellfish	less vs. several times a week	thyroid cancer	age ≤ 20 years: 1.0 (0.2–6.9); age > 20 years: 1.6 (0.3–8.7)
Mack, W. J. (2002)	case-control study	the United States	case:292 control:292	15–54 (F)	shellfish	less than a few times yearly vs. at least a few times weekly	all types of thyroid cancer; papillary thyroid cancer	0.8 (0.3–2.4); 0.6 (0.2–2.1)
Hornross, P. L. (2001)	case-control study	the United States	case:608 control:558	20–74 (F)	shellfish	< 1.0 g/d vs. >7.5 g/d	papillary thyroid cancer	0.93 (0.64–1.3)
Kolonel, L. (1990)	case-control study	the United States	case:191 control:441	>18 (both)	shellfish	low vs.high	thyroid cancer	Male: 1.1 (0.4–2.7); Female: 0.9 (0.6-1.5)
Memon, A. (2002)	case-control study	Kuwait	case:311 control:311	< 70 (both)	shellfish	Low (never or occasional -few times a year) vs. High (2-4 days per week or 5-7 days per week)	thyroid cancer	1.2 (0.7–2.0)
Cléro, É. (2012)	case-control study	French Polynesia	case:229 control:371	10–62 (both)	shellfish	0 vs.≥8g/d	differentiated thyroid cancer	0.40 (0.22–0.72)
Ren, Y. (2016)	case-control study	Cuba	case:203 control:212	17-60	shellfish	0 vs. ≥5 g/d	thyroid cancer	0.70 (0.43–1.13)
Zamora-Ros, R. (2017)	cohort study	Europe	476,108	35–70 (both)	shellfish	0.8g/d vs. >4.1 g/d	differentiated thyroid cancer	1.42 (0.78–2.59)
Lee, S. A. (2009)	cohort study	China	73,224	40–70 (F)	crustaceans, mollusks	0 vs. ≥0.6 g/d	colorectal cancer, colon cancer	1.3 (1.0–1.6)
Chen, F. (2017)	case-control study	China	case:930 control:2,667	20–80 (both)	seafood other than fish (shrimp/ crab/shellfish	< 3 times/wk vs. ≥3 times/wk	oral cancer	1.99 (1.65–2.40)
He, K. (2013)	cohort study	the United States	66,616	50–76 (both)	shellfish	< 0.175 servings/wk vs. ≥0.290 servings/wk	pancreatic cancer	1.45 (0.94–2.23)
Pelé, F. (2013)	cohort study	France	1,500	Child (2 years old)	shellfish	<1 time / mo vs. ≥1 time / mo	probable wheeze; certain wheeze; eczema; food allergy	1.08 (0.83–1.40); 1.08 (0.78–1.49); 1.09 (0.85–1.40); 1.62 (1.11–2.37)
Leermakers, E. T. (2013)	cohort study	Netherlands	2,796	child	shellfish	0; vs. >14 g/wk	Wheezing; eczema	1.06 (0.92–1.22); 1.02 (0.86, 1.21)

secretion regulate uric acid excretion (Chaudhary et al. 2013). The purine content of shellfish is generally believed to cause hyperuricemia and gout. Gout is a genetic disease, but it is still closely related to diet (Nyhan 2005). Shrimps are rich in hypoxanthine and adenine. Adenine, guanine, and hypoxanthine contents are equivalent in shellfish, whereas squid, clams, and oysters contain higher xanthine content (Qu et al. 2017). Because most patients with gout have weaker renal uric acid clearance than those with normal blood uric acid, eating a large amount of purines can increase serum uric acid levels (Choi et al. 2005; Lee et al. 2006).

Cardiovascular diseases

Cardiovascular diseases include coronary heart disease, myocardial infarct, and heart failure. Approximately 17.9 million people died from cardiovascular diseases in 2016, representing 31% of all global deaths, and 85% of those were due to stroke and heart attack (World Health Organization 2016). In some countries, rapid economic development is accompanied by a transition to the Western dietary pattern. The dietary change is considered to, at least in part, have contributed to a higher cardiometabolic risk profile among healthy young adults in China (Wan et al. 2017). Four studies have evaluated the relationship between shellfish consumption and cardiovascular diseases (Matheson et al. 2009; Myint et al. 2006; Yuan et al. 2001; Durga and Manorenj 2019). Three prospective cohort studies concluded that shellfish consumption was not related to the risk of cardiovascular diseases. One case–control study in India found that shrimp and crab consumption in stroke patients (median value: 29 g/week) was lower than that of healthy controls (median value: 45 g/week) (OR = 0.55; 95% CI, 0.32–0.95). In addition, one experimental study on the relationship between shrimp intake and cardiovascular disease demonstrated that healthy men eating Arctic shrimp for 12 weeks had no change in their plasma cholesterol, triglyceride, and lipoprotein levels (Isherwood et al. 2010). Much evidence supports the recommendation to consume nonfried seafood, especially species higher in n-3 LC-PUFA, 1-2 times per week for cardiovascular benefits, including reduced risk of cardiac death, coronary heart disease, and ischemic stroke (Rimm et al. 2018). Increased dietary n-3 LC-PUFA intake enhances arterial elasticity by increasing endothelium-derived vasodilators (Cottin et al. 2011), including nitric oxide, 3-series prostacyclin, and endothelium-dependent hyperpolarizing factor. A meta-analysis of 16 randomized controlled trials concluded that n-3 LC-PUFA supplementation significantly improved endothelial function (Wang et al. 2012).

Endometriosis

Endometriosis is a benign, estrogen-dependent, gynecologic condition found in approximately 10% of women of reproductive age (Wheeler 1989). It is characterized by the presence of endometrial tissue outside of the uterus, causing inflammation, scars, and adhesions. One prospective cohort study of premenopausal American nurses indicated that shellfish consumption (≥2 times/week vs. <1 times/month) was not significantly associated with endometriosis (RR = 1.04; 95% CI, 0.79–1.38) (Yamamoto et al. 2018). How diet affects endometriosis remains poorly understood but may involve circulating steroid hormones (Missmer and Cramer 2003).

Hip fracture

Hip fractures are the most severe complication of osteoporosis and have attracted increased attention because of poor prognosis, such as leading to chronic pain and increasing the risk of disability (Leibson et al. 2002). One case–control study (Fan et al. 2013) revealed that shellfish consumption had a significant protective effect against hip fracture risk in the elderly population (OR = 0.55; 95% CI, 0.34–0.88). The beneficial effects of shellfish may be due to the high-bioavailability protein it contains and the lower acid load generated by the displacement of meat protein. Another essential nutrient that may affect this association is calcium. Calcium is the key nutrient for bone health, because the bone–parathyroid–kidney–ileum axis is finely tuned for the maintenance of physiological calcium and phosphorous levels and bone tissue renewal (Blau and Collins 2015). Moreover, calcium is essential for muscle physiology as it regulates the contraction and relaxation of myosin fibers as well as glycolytic and mitochondrial metabolism in the muscle fibers (Kuo and Ehrlich 2015; Gehlert et al. 2015). Therefore, adequate calcium status is essential for both bone and muscle. A meta-analysis of 18 observational studies reported a negative association between dietary calcium and hip fracture risk among older women (OR = 0.96; 95% CI, 0.93–0.99) (Cumming and Nevitt 1997). This is likely to underestimate calcium's true effect because dietary calcium is often inaccurately measured in observational studies. However, one meta-analysis of 33 randomized clinical trials including 51,145 participants indicated that supplementation with calcium, vitamin D, or both did not significantly affect hip fracture risk compared with placebo or no treatment (Zhao et al. 2017). Currently, no consistent evidence of a relationship between dietary calcium intake and risk of fracture is available. Individuals at high risk of fracture should be offered treatments proven to prevent fracture with a favorable risk–benefit profile (Chiodini and Bolland 2018).

Cognitive function

One cohort study (Grattan et al. 2016) suggested that individuals who consume very high amounts of razor clams (>15 razor clams/month) perform worse on memory measures than a reference group of nonconsumers or low consumers (<15 razor clams/month). This is caused by domoic acid accumulation in shellfish. Extensive research has concluded that razor clams are the most significant vector for domoic acid because they retain the toxin for up to 1 year in the natural environment or for several years after being processed, canned, or frozen (Wekell et al. 1994). Domoic acid exposure primarily affects the hippocampal regions of the brain, causing transient and permanent changes in memory function that resemble human antegrade amnesia (Grant et al. 2010), leading to seizures and cognitive disruption. Unlike the permanent cognitive impacts of acute exposure, the chronic low-level effects were reversible, suggesting that these deficits could be managed through cessation of exposure if they also occur in human seafood consumers (Lefebvre et al. 2017).

Thyroid cancer

Thyroid cancer has five main histological types: papillary, follicular (also known as differentiated), poorly differentiated, anaplastic, and medullary thyroid cancer (Seib and Sosa 2019). The incidence of thyroid cancer worldwide has increased significantly over the past three decades due predominantly to an increase in papillary thyroid cancer (Chmielik et al. 2018). Twelve studies have reported a relationship between shellfish consumption and thyroid cancer, including two meta-analyses (Liu and Lin 2014; Cao et al. 2017), nine case–control studies (Kolonel et al. 1990; Preston-Martin et al. 1993; Wingren et al. 1993; Hallquist et al. 1994; Hornross et al. 2001; Mack et al. 2002; Memon et al. 2002; Cléro et al. 2012; Ren et al. 2016), and one prospective cohort study (Zamora-Ros et al. 2017). One case--control study from French Polynesia (Cléro et al. 2012), an iodine-deficient area, believed that shellfish consumption ($\geq$8 g/day) had a protective effect against differentiated thyroid cancer. None of the remaining eight case–control studies and one prospective cohort study found a statistical association between the two. One meta-analysis (Liu and Lin 2014) involving nine case–control studies found no statistical association between shellfish, shrimp, and crab intake and thyroid cancer (OR = 0.88; 95% CI, 0.72–1.08). A subgroup analysis stratified by iodine-deficient regions revealed that shellfish consumption protected against thyroid cancer in iodine-deficient areas (OR = 0.46; 95% CI, 0.27–0.75) but not in iodine-rich areas. Another meta-analysis (Cao et al. 2017) involving three case–control studies found that high shellfish consumption ($\geq$3 times/week) can reduce the risk of thyroid cancer (OR = 0.70; 95% CI, 0.52–0.96), probably due to the rich iodine in shellfish, which is very high at >120 μg/100 g (Cléro et al. 2012). One meta-analysis concluded that a higher iodine intake ($\geq$300 μg/day) and high consumption of saltwater fish and shellfish were protective factors against thyroid cancer (Cao et al. 2017). As an essential trace element for thyroid function, iodine plays an indispensable role in growth and metabolism throughout human life (Laurberg et al. 2001).

Colorectal cancer and Colon cancer

Colorectal cancer is the most commonly diagnosed cancer globally, and its incidence increases with age. Approximately 41% of all colorectal cancers occur in the proximal colon, followed by the distal colon (22%) and rectum (28%) (Cheng et al. 2011). One prospective cohort study (Lee et al. 2009) of women aged 40–70 years in Shanghai, China, reported that shellfish consumption ($\geq$0.6 g/day vs. 0 g/day) was positively correlated with the incidence of colorectal cancer (RR = 1.3; 95% CI, 1.0–1.6) and colon cancer (RR = 1.4; 95% CI, 1.0–1.9). Shrimp consumption ($\geq$14.6 g/day vs. <2.4 g/day) was positively correlated with the incidence of colorectal cancer (RR = 1.3; 95% CI, 1.0–1.9). This may be because shellfish are rich in cholesterol, which is converted into bile acids. A high total cholesterol level is associated with a higher risk of colon cancer (Kitahara et al. 2011). Another study considering genetic factors confirmed the link between hypercholesterolemia and colorectal cancer risk (Rodriguez-Broadbent et al. 2017). Abnormally high secondary bile acid concentrations trigger numerous detrimental effects within the colonic mucosa, such as oxidative stress and inflammation (Stadler et al. 1988; Vaughn et al. 2019). Total bile acids, especially deoxycholic acid and lithocholic acid, are well known as toxic bile acids to colonic cells. They induce cell death by involving death receptors or mitochondria (Zeng et al. 2019). These processes could cause the transition of cells into a precancerous state and are considered an early priming step in colorectal tumorigenesis. The main source of mercury exposure is food such as fish and shellfish. One case–control study indicated that a high intake of dietary mercury was associated with an elevated risk of overall colorectal cancer (Kim et al. 2020).

Oral cancer

The oral cavity is the frequent site of upper aerodigestive tract malignancies. Squamous cell carcinoma (95%) is the most common histological type of oral cancer (Paré and Joly 2017; D'souza and Addepalli 2018). A case–control study (Chen et al. 2017) indicated that less intake of seafood other than fish (shrimp, crab, or shellfish) (<3 times/week) significantly increased the risk of oral cancer (OR = 1.99; 95% CI, 1.65–2.40). Shellfish contain LC-PUFA, mineral salts, and proteins that could inhibit tumor progression through their anti-inflammatory effects and inhibition of oxygen free radicals (MacLean et al. 2006).

Pancreatic cancer

Pancreatic cancer is a lethal malignancy. The lifetime risk of pancreatic cancer is 1.49%, which is approximately one in 67 cases (Becker et al. 2014). One prospective cohort study (He et al. 2013) in Washington revealed that shellfish consumption was not significantly associated with the risk of pancreatic cancer (HR = 1.45; 95% CI, 0.94–2.23); however, this study also found that intakes of n-3 LC-PUFA, particularly DHA, were inversely related to pancreatic cancer incidence. Substantial evidence has highlighted that these fatty acids can partly inhibit many aspects of inflammation, including leucocyte chemotaxis, adhesion molecule expression, leucocyte–endothelial adhesive interactions, and production of inflammatory cytokines (e.g., Tumour Necrosis Factor alpha) (Calder 2017).

Wheeze, eczema and food allergy

Approximately 0.5%–2.5% of the general population has shellfish allergy, but higher proportions are noted in coastal Asian countries where shellfish consumption is considerably higher. Allergens include tropomyosin, arginine kinase, myosin light chain, and sarcoplasmic binding protein from crustaceans and tropomyosin, paramyosin, troponin, actin, amylase, and hemocyanin from mollusks. To summarize, adverse reactions to seafood are often due to toxins or microbial contaminants but can also be mediated by allergens (Ruethers et al. 2018; Khora 2016).

One prospective cohort study in Brittany, France (Pelé et al. 2013) indicated that maternal shellfish consumption was not associated with probable wheeze (OR = 1.08; 95% CI, 0.83–1.40), certain wheeze (OR = 1.08; 95% CI, 0.78–1.49), eczema (OR = 1.09; 95% CI, 0.85–1.40); however, shellfish consumption once a month or more was associated with a higher risk of a food allergy (OR = 1.62; 95% CI, 1.11–2.37). Another prospective cohort study in the Netherlands (Leermakers et al. 2013) found that maternal shellfish consumption of 1–13 g/week was associated with overall increased risks of childhood wheezing (OR = 1.06; 95% CI, 0.92–1.22) and eczema (OR = 1.18; 95% CI, 1.01–1.37).

Future research needs and key questions

First, although the studies discussed in this review were human studies rather than animal or experimental studies, the strength of evidence was inconsistent due to different study designs (Rothman 2014). Although shellfish provide several nutrients to the diet, their protective effects against certain chronic noncommunicable diseases are largely observational. Future well-designed studies with large sample sizes are required to definitively conclude these effects.

Second, many studies have explored the association between diet and disease in the form of seafood or fish/shellfish directly (McClain et al. 2019; Talaei et al. 2017; Teng et al. 2015). EPA and DHA are present mainly in fatty shellfish; thus, it is vital to consider the type of shellfish consumed (Suematsu et al. 2013) instead of total shellfish consumption alone. Defining intake with more precise measures (e.g., grams) rather than the subjective measure of "servings" will help researchers better compare outcomes among various studies. Furthermore, more sophisticated measurement measures may be needed rather than relying solely on participants' memory.

Third, biomarkers not only indicate health status from a prevention standpoint but also help ascertain compliance among intervention studies (Cuparencu et al. 2019; Guertin et al. 2014; Lu et al. 2017; Childs et al. 1990). However, limited biomarkers (e.g., n-3 LCPUFA, trimethylamine-N-oxide, furan fatty acids) are available (Cuparencu et al. 2019), and those that are available are difficult to interpret because of other factors contributing to biomarker exposure. However, a review indicated that no specific biomarkers arose from separate search on shellfish (Cuparencu et al. 2019). Gene–nutrient interaction studies that measure genetic variants in relevant genes are required to develop individualized nutrition recommendations.

Fourth, few epidemiological studies have considered preparation methods. Many studies or case reports have indicated that eating raw oysters, shrimps, or crabs increases the risk of acute gastroenteritis. However, educational strategies (e.g., warning messages) may not reach all potential cases (Mouzin et al. 1997); more effective consumer education and additional regulatory measures are warranted to further reduce the incidence of shellfish-associated food poisoning. Of note, frying, especially deep frying, may substantially reduce the n-3 LC-PUFA content (Echarte et al. 2001) and generate harmful chemicals such as heterocyclic amines and benzo(a)pyrene; combining fried and nonfried shellfish consumption may attenuate or mask any possible association.

Finally, shellfish consumption is not only a nutrition or hygiene problem but also related to environmental protection, necessitating multiparty cooperation. Prevention of seafood-associated infections requires an understanding of the etiologic agents and seafood commodities associated with illness as well as preventable or controllable mechanisms of contamination. Robust monitoring of ocean pollution is vital for protecting human health and safeguarding marine ecosystems, and better documentation of pollution-related patterns of human exposure and disease will improve estimates of the contribution of ocean pollution to the Global Burden of Disease (Landrigan et al. 2020). The Food and Drug Administration has established the Hazard Analysis and Critical Control Points program (Food and Drug Administration 2018). These programs have effectively minimized human illnesses due to toxic shellfish consumption while allowing fisheries industries to persist in regions threatened by recurrent harmful algal blooms.

Conclusions

Shellfish consumption may increase the risk of hyperuricemia and gout and may not be associated with an increased risk of type 2 diabetes, cardiovascular diseases, and thyroid cancer. However, insufficient evidence exists to definitively determine an association between shellfish consumption and the risk of diseases such as colorectal cancer, pancreatic cancer, oral cancer, endometriosis, hip fracture, cognitive function, wheeze, eczema and food allergy. Raw shellfish consumption may cause gastroenteritis and other diseases due to toxins or infections by bacteria or viruses. This review thus provides consumers and other relevant stakeholders with the latest evidence-based information on the potential benefits and risks of shellfish consumption. However, the majority of evidence linking shellfish consumption to chronic disease prevention is observational and cannot be used to establish causality. In the future, well-designed studies with large sample sizes are required to definitively conclude these effects.

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