9
Cholesterol

SUMMARY

Cholesterol plays an important role in steroid hormone and bile acid biosynthesis and serves as an integral component of cell membranes. Given the capability of all tissues to synthesize sufficient amounts of cholesterol for their metabolic and structural needs, there is no evidence for a biological requirement for dietary cholesterol. Therefore, neither an Adequate Intake nor a Recommended Dietary Allowance is set for cholesterol.

There is much evidence to indicate a positive linear trend between cholesterol intake and low density lipoprotein cholesterol concentration, and therefore increased risk of coronary heart disease (CHD). A Tolerable Upper Intake Level is not set for cholesterol because any incremental increase in cholesterol intake increases CHD risk. Because cholesterol is unavoidable in ordinary diets, eliminating cholesterol in the diet would require significant changes in patterns of dietary intake. Such significant adjustments may introduce undesirable effects (e.g., inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. Nonetheless, it is possible to have a diet low in cholesterol while consuming a nutritionally adequate diet. Dietary guidance for minimizing cholesterol intake is provided in Chapter 11.

BACKGROUND INFORMATION

Function

Cholesterol is a sterol that is present in all animal tissues. Tissue cholesterol occurs primarily as free (unesterified) cholesterol, but is also bound covalently to fatty acids as cholesteryl esters and to certain proteins. Free cholesterol is an integral component of cell membranes and serves as a precursor for steroid hormones such as estrogen, testosterone, and aldosterone, as well as bile acids.

Physiology of Absorption and Metabolism

Absorption

After emulsification and bile acid micellar solubilization, dietary cholesterol, as well as cholesterol derived from hepatic secretion and sloughed intestinal epithelium, is absorbed in the proximal jejunum. Cholesteryl esters, comprising 10 to 15 percent of total dietary cholesterol, are hydrolyzed by a specific pancreatic esterase. Cholesterol absorption by enterocytes is believed to occur primarily by passive diffusion across a concentration gradient established by the solubilization of cholesterol in bile acid micelles. However, recent evidence has shown that scavenger receptor class B type I is present in the small intestine brush-border membrane where it facilitates the uptake of micellar cholesterol (Hauser et al., 1998). In addition, as described further below, two recently identified adenosine triphosphate binding-cassette (ABC) proteins (ABCG5 and ABCG8) have been found to form heterodimers that export plant sterols and cholesterol from enterocytes into the gut lumen, thereby decreasing net sterol absorption (Berge et al., 2000). ABC1, a transporter involved in high density lipoprotein–(HDL) mediated cellular cholesterol efflux, may also participate in this process (Repa et al., 2000).

Esterification of cholesterol and subsequent secretion of both esterified and unesterified cholesterol into lymph and plasma in intestinally synthesized chylomicron and HDL particles may also affect net cholesterol uptake by enterocytes. Key components of this process include cholesterol esterification by acylCoA:cholesterol acyltransferase; lipoprotein assembly with the structural protein apoB48 (chylomicrons) and apoAI (HDL), as well as with triacylglycerols and phospholipids; and lipoprotein secretion into lymphatics facilitated by microsomal triacylglycerol transfer protein.

Cholesterol balance studies in humans have indicated a wide variation in efficiency of intestinal cholesterol absorption (from 20 to 80 percent), with most individuals absorbing between 40 and 60 percent of ingested

cholesterol (Ros, 2000). As discussed below, such variability, which is likely due in part to genetic factors, may contribute to interindividual differences in plasma cholesterol response to dietary cholesterol. In addition, cholesterol absorption may be reduced by the cholesterol content of a meal and by decreased intestinal transit time (Ros, 2000). Although fatty acids are required for intestinal micelle formation, there is no strong evidence that fat content (or other dietary constituents such as fiber) has a significant effect on cholesterol absorption.

An average of 250 mg/d of plant sterols (e.g., sitosterol, stigmasterol, and campesterol) are consumed in the diet, but the absorption of such sterols (approximately 5 percent) is considerably lower than that for cholesterol (Ling and Jones, 1995; Salen et al., 1970). They are not known to have important biological effects in humans at the levels consumed in the diet. An exception is sitosterolemia, a rare genetic disorder that is characterized by markedly increased absorption and tissue accumulation of plant sterols and elevated plasma cholesterol levels (Lütjohann et al., 1996; Salen et al., 1992). Recently, patients with this disorder have been shown to have mutations in genes encoding ABCG5 and ABCG8, indicating the importance of these transporters in regulating sterol absorption presumably by promoting the export of nearly all plant sterols, and a portion of cholesterol, from intestinal cells (Berge et al., 2000). Moreover, increased expression of these genes induced by cholesterol feeding may be of importance in limiting cholesterol absorption (Berge et al., 2000). The ability of very high intakes of plant sterols to lower plasma cholesterol concentrations by reducing cholesterol absorption may also involve regulation of this transport process (Miettinen and Gylling, 1999).

Metabolism

Intestinally derived cholesterol is transported in the circulation to other tissues via chylomicrons, and to a lesser extent HDL, mainly in the form of cholesteryl ester. The hydrolysis of chylomicron triacylglycerols in peripheral tissues by lipoprotein lipase and subsequent remodeling by lipid transfer proteins yields a "remnant" particle that is internalized by receptors, primarily in the liver, that recognize apoprotein E and perhaps other constituents. Cholesterol released by intracellular cholesteryl esterase activity can be stored in hepatocytes; re-esterified and secreted into plasma in lipoproteins, primarily very low density lipoproteins (VLDL); oxidized and excreted as bile acids; or directly secreted into the bile. Free and esterified cholesterol circulate in the blood in humans principally in low density lipoproteins (LDL).

Cholesterol homeostasis in hepatocytes is of critical importance for the regulation of plasma LDL cholesterol concentrations (Dietschy et al.,

1993). Increased cellular cholesterol content leads to suppression of synthesis of LDL receptors via a series of steps resulting in interaction of sterol regulatory element-binding protein (SREBP) 1 and 2 transcription factors with a sterol response element in the LDL receptor gene (Brown and Goldstein, 1999). Increased plasma LDL concentrations can result from reduced hepatic LDL uptake, as well as reduced uptake of VLDL and intermediate density lipoproteins, leading to increased metabolic conversion of these particles to LDL (Kita et al., 1982). Metabolic studies in humans have indicated that a high cholesterol diet induces both increased LDL synthesis and reduced receptor-dependent fractional removal rate of LDL particles (Packard et al., 1983).

There are a number of other genes involved in cholesterol and lipoprotein metabolism in which hepatic regulation can be affected by cholesterol availability either directly via SREBPs or indirectly by the action of other transcription factors, such as liver X receptors (Repa and Mangelsdorf, 2000). These genes play a role in cholesterol regulatory pathways, including those involved in cholesterol synthesis that are suppressed by cholesterol (e.g., 3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase) and others involved in bile acid production from cholesterol that are activated by cholesterol (e.g., 7 α-hydroxylase). Thus, increased hepatic cholesterol delivery from diet and other sources results in a complex admixture of metabolic effects that are generally directed at maintaining tissue and plasma cholesterol homeostasis. However, as described below, empirical observations in humans have indicated that increased dietary cholesterol does result in a net increase in plasma LDL cholesterol concentrations, probably as a consequence of reduced hepatic LDL receptor activity.

All cells are capable of synthesizing cholesterol in sufficient amounts for their structural and metabolic needs. However, certain tissues (e.g., adrenal glands and gonads) derive a significant proportion of cholesterol by uptake from plasma lipoproteins. Cholesterol synthesis via a series of intermediates from acetyl CoA is highly regulated. The enzyme HMG CoA reductase catalyzes the rate-limiting step in cholesterol synthesis—the formation of mevalonic acid from HMG CoA. The genes for this enzyme and a number of other proteins involved in cholesterol metabolism, such as the LDL receptor, are regulated by intracellular sterols and other signaling molecules to maintain tissue cholesterol homeostasis, as described above. Endogenous cholesterol synthesis in humans is approximately 12 to 13 mg/kg/d (840 to 910 mg/d for a 70-kg individual) (Di Buono et al., 2000).

Another group of diet-derived sterols with potential biological effects are oxysterols (Vine et al., 1998), which are cholesterol oxidation products that can be found in cholesterol-rich processed foods such as dried egg yolk, although typical levels of oxysterols in the diet are generally low

(van de Bovenkamp et al., 1988). These cholesterol oxidation products can have major effects on cholesterol metabolism and have been shown to be highly atherogenic in animal models (Staprans et al., 2000; Vine et al., 1998). Their role in human nutrition remains to be established.

Overall, body cholesterol homeostasis is highly regulated by balancing intestinal absorption and endogenous synthesis with hepatic excretion of cholesterol and bile acids derived from hepatic cholesterol oxidation.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Given the capability of all tissues to synthesize sufficient cholesterol for their metabolic and structural needs, there is no evidence for a biological requirement for dietary cholesterol. As an example, many Tarahumara Indians of Mexico consume very low amounts of dietary cholesterol and have no reported developmental or health problems that could be attributed to this aspect of their diet (McMurry et al., 1982). Therefore, neither an Adequate Intake (AI) nor an Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) are set for cholesterol.

The question of whether cholesterol in the infant diet plays some essential role on lipid and lipoprotein metabolism that is relevant to growth and development or to the atherosclerotic process in adults has been difficult to resolve. The idea that the early diet might have relevance to later lipid metabolism was first raised by Hahn and Koldovský (1966) in prematurely weaned rat pups and later supported by observations that normal weaning to a high intake of cholesterol resulted in greater resistance to dietary cholesterol in later adulthood (Reiser and Sidelman, 1972; Reiser et al., 1979). This led to the hypothesis that cholesterol in human milk may play some important role in establishing regulation of cholesterol homeostasis. Since human milk typically provides about 100 to 200 mg/L (Table 9-1), whereas infant formulas contain very little cholesterol (10 to 30 mg/L) (Huisman et al., 1996; Wong et al., 1993), it is not surprising that plasma cholesterol concentrations are higher in infants fed human milk than in formula-fed infants. Formula-fed infants also have a higher rate of cholesterol synthesis (Bayley et al., 1998; Cruz et al., 1994; Wong et al., 1993). However, the available evidence suggests that this effect is transient. Differences in cholesterol synthesis and plasma cholesterol concentration are not sustained once complementary feeding is introduced (Darmady et al., 1972; Friedman and Goldberg, 1975; Mize et al., 1995). Also, no clinically significant effects on growth and development due to these differences in plasma cholesterol concentration have been noted between breast-fed and formula-fed infants under 1 year of age. One explanation may be that the developing brain synthesizes the cholesterol required for myelination in situ and does not take up cholesterol from

TABLE 9-1 Cholesterol Content in Term Human Milk of Women in the United States

Reference	*n*	Stage of Lactation	Cholesterol Content (mg/L)
Picciano et al., 1978	18	6–12 wk postpartum (pp)	
		Early morning	157
		Midday	151
		Evening	178
Mellies et al., 1979	33	1 mo pp	201
		2 mo pp	195
		3 mo pp	97
		4 mo pp	220
		5 mo pp	156
		6 mo pp	283
		7 mo pp	289
		8 mo pp	220
		9 mo pp	260
		10 mo pp	210
		11 mo pp	135
		12–13 mo pp	151
Clark et al., 1982	10	2 wk pp	110
		6 wk pp	97
		12 wk pp	103
		16 wk pp	104
Bitman et al., 1983	6	3 wk pp	122
		6 wk pp	112
		12 wk pp	103
Lammi-Keefe et al., 1990	6	8 wk pp	
		0600 h	88
		1000 h	107
		1400 h	111
		1800 h	110
		2200 h	112
Jensen et al., 1995	10	12 wk pp	
		0600–1000 h	140
		1000–1400 h	162
		1400–1800 h	217
		1800–2200 h	220
		2200–0600 h	129
Bayley et al., 1998	14	4 mo pp	120

plasma (Edmond et al., 1991; Haave and Innis, 2001; Jurevics and Morell, 1994).

The effects of early cholesterol intake and weaning on cholesterol metabolism later in life have been studied in a number of different animal species (Hamosh, 1988; Kris-Etherton et al., 1979; Mott et al., 1990) and in short-term studies with infants and children. Studies in baboons fed breast milk or formulas with or without cholesterol and with varying fat compositions found that early cholesterol intake had little effect on serum cholesterol concentrations in young adults up to about 8 years of age (Mott et al., 1990). However, adult baboons that had been breast fed had lower high density lipoprotein (HDL) cholesterol concentrations, higher very low density lipoprotein + low density lipoprotein (LDL):HDL ratios, and more extensive atherosclerotic lesions than those that had been formula fed (Lewis et al., 1988; Mott et al., 1990, 1995). These differences were not explained by variations in the saturated and unsaturated fat content of the formulas and milk. The major metabolic difference associated with the differences in plasma lipoproteins was lower rates of bile acid synthesis and excretion among the baboons that had been breast fed.

The possible relations of early breast and bottle feeding with later cholesterol concentrations and other coronary heart disease risk factors were explored in several short-term studies and larger retrospective epidemiological studies, but these observations are inconsistent (Fall et al., 1992; Kolaček et al., 1993; Leeson et al., 2001; Ravelli et al., 2000).

The relationship between early dietary cholesterol intake from milk or formula and serum cholesterol concentration in infancy and that observed in children and young adults following their usual diets was either absent (Andersen et al., 1979; Friedman and Goldberg, 1975; Glueck et al., 1972; Huttunen et al., 1983), in favor of formula feeding compared to breast feeding during infancy in 7- to 12-year-old children (Hodgson et al., 1976), or in favor of feeding human milk compared to formula feeding in men and women. The disparate findings may be due to confounding factors such as duration of breast feeding, since human-milk feeding for less than 3 months was associated with higher serum cholesterol concentrations in men at 18 to 23 years of age, or the type of formula fed since formula composition, especially quality of fat, which has changed dramatically in the last century (Kolaček et al., 1993). A follow-up study of nearly 6,000 elderly men for whom early feeding methods had been recorded found higher total and LDL cholesterol concentrations and increased risk of coronary heart disease (CHD) mortality in men who had been exclusively fed human milk than in those who had been fed human milk and bottle fed or fed human milk and weaned at 1 year of age. Men who had been exclusively bottle-fed during infancy also had higher total and LDL choles-

terol concentrations and CHD mortality than men who had previously been fed human milk (Fall et al., 1992).

The available data do not warrant a recommendation with respect to dietary cholesterol intake for infants who are not fed human milk. However, further research to identify possible mechanisms whereby early nutritional experiences affect the atherosclerotic process in adults, as well as the sensitive periods in development when this may occur, would be valuable.

INTAKE OF CHOLESTEROL

Food Sources

Cholesterol is present in foods of animal origin. High amounts of cholesterol are present in liver (375 mg/3 oz slice) and egg yolk (250 mg/yolk). Although generally low in total fat, some seafood, including shrimp, lobster, and certain fish, contain moderately high amounts of cholesterol (60 to 100 g/half-cup serving). One cup of whole milk contains approximately 30 mg of cholesterol, whereas the cholesterol contained in 2 percent and skim milk is 15 and 7 mg/cup, respectively. Therefore, products that contain milk (e.g., cheese, ice cream, and cottage cheese) are moderate sources of cholesterol. One tablespoon of butter contains approximately 12 mg of cholesterol, whereas margarine does not contain cholesterol. The majority of cholesterol is consumed from eggs and meat (FASEB, 1995).

Dietary Intake

Based on intake data from the Continuing Survey of Food Intakes by Individuals (1994–1996, 1998), the median cholesterol intake ranged from approximately 250 to 325 mg/d for men and 180 to 205 mg/d for women (Appendix Table E-15).

ADVERSE EFFECTS OF OVERCONSUMPTION

Hazard Identification

Plasma Total, HDL, and LDL Cholesterol Concentrations

Numerous studies in humans have examined the effects of dietary cholesterol on plasma total and lipoprotein cholesterol concentrations (Tables 9-2 and 9-3, Figures 9-1 and 9-2), and empirical formulas have been derived to describe these relationships. Although most studies have

TABLE 9-2 Effects of Adding Dietary Cholesterol to Defined Diets with Strict Control of Dietary Intake on Serum Cholesterol Concentration

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Beveridge et al., 1960	6	13	81
	9	13	140
	9	13	280
	9	13	621
	6	13	1,282
	10	13	2,481
	9	13	4,490
Connor et al., 1961a	2	0	475
	2	0	950
	2	0	1,425
Connor et al., 1961b	3	0	2,400
	1	0	1,650
	1	0	1,900
	1	0	4,800
Steiner et al., 1962	6	0	3,000
Wells and Bronte-Stewart, 1963	3	0	17
	3	0	42
	3	0	67
	3	0	88
	3	0	142
	3	0	267
	3	0	517
	3	0	1,017
	3	0	1,517
	3	0	3,017
Connor et al., 1964	6	0	729
	5	0	725
Erickson et al., 1964	6	0	742
	6	0	742
Hegsted et al., 1965	10	116	570
	10	306	380
	10	116	570

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.06	30	0.08
0.10	30	0.08
1.17	30	0.08
0.43	30	0.08
0.59	30	0.08
1.20	30	0.08
0.87	30	0.08
1.71	40	0.76
1.64	40	0.76
1.99	40	0.76
1.47	40	0.88
2.43	40	0.88
2.97	40	0.88
2.53	40	0.88
1.30	40	0.68
0.44	15	
0.56	15	
0.66	15	
0.80	15	
0.96	15	
1.03	15	
1.18	15	
1.09	15	
1.29	15	
1.23	15	
1.03	40	0.25
0.74	40	1.7
0.61	41	1.6
0.69	41	1.6
0.75	39	5.4
0.29	39	0.05
0.70	39	0.68

continued

TABLE 9-2 Continued

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Keys et al., 1965	22	50	470
	22	50	1,410
	22	50	33
	22	50	1,400
	22	50	1,410
National Diet-Heart Study Research Group,1968	81	126	495
	81	126	495
	57	401	495
	57	154	495
Quintão et al., 1971	4	43	2,441
	1	43	499
	1	44	197
	2	53.5	4,002
Mattson et al., 1972	14	0	297
	14	0	594
	14	0	888
Anderson et al., 1976	12	3	291
	12	3	291
Nestel and Poyser, 1976	4	210	500
	2	257	500
	2	334	532
	1	103	439
Quintão et al., 1977	6	0	3,250
Bronsgeest-Schoute et al., 1979a, 1979b	21	98	567
	21	98	567
	9	124	607
	9	124	607
Lin and Connor, 1980	2	45	1,081
McMurry et al., 1981	12	0	600

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.36	40	
0.70	40	
0.41	40	
0.80	40	1.3
0.75	40	0.08
0.12	30	2.31
0.27	39	0.5
0.32	40	0.08
0.18	40	0.96
0.96	40	0.93
0.88	40	0.93
–0.80	40	0.93
0.13	40	0.93
0.34	39	0.31
0.61	39	0.31
1.05	39	0.31
0.23	35	0.26
0.21	35	4.7
1.56	40	1.9
0.25	40	1.9
0.76	40	1.9
0.67	40	1.9
0.74		
0.32	44	2
0.25	44	2
0.70	34	0.2
0.66	34	0.2
2.45	40	0.8
0.93	40	0.8

continued

TABLE 9-2 Continued

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
McMurry et al., 1982	8	0	905
Nestel et al., 1982	6	200	1,500
Schonfeld et al., 1982	11	300	750
	9	300	1,500
	6	300	750
	6	300	1,500
	6	300	750
	6	300	1,500
Maranhão and Quintdo, 1983	13	40	1,350
Applebaum-Bowden et al., 1984	9	137	897
Beynen and Katan, 1985b	6	114	526
Katan et al., 1986	94	110	500
Zanni et al., 1987	9	130	745
	9	130	745
Johnson and Greenland, 1990	10	200	400
Ginsberg et al., 1994	20	128	155
	20	128	340
	20	128	730
Sundram et al., 1994	17	192	7
	17	192	13
Fielding et al., 1995	20	200	403
	22	200	435
Ginsberg et al., 1995	13	108	169
	13	108	559

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.88	20	0.7
0.42	31	1
0.47	40	0.32
0.72	40	0.32
0.13	40	0.8
0.70	40	0.8
0.05	40	2.5
0.26	40	2.5
1.19	40	0.93
0.28	40	0.82
0.25	42	0.46
0.5	42	0.16
0.58	31	2.1
0.39	31	0.64
0.26	30	1.5
0.14	27	0.89
0.16	27	0.93
0.29	28	0.87
0.06	31	0.21
–0.35	31	0.25
0.50	39	0.81
0.76	36	0.28
0.16	28	0.89
0.41	28	0.86

TABLE 9-3 Effects of Adding Dietary Cholesterol to Self-Selected Diets with Strict Control of Dietary Intake on Serum Cholesterol Concentration

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Slater et al., 1976	25	314	482
Kummerow et al., 1977	21	250	470
Porter et al., 1977	55	301	235
	59	301	235
Flynn et al., 1979	56	260	540
	60	260	540
Mistry et al., 1981	37	522	1,500
	14	480	750
Roberts et al., 1981	16	196	532
Packard et al., 1983	7	180	1,290
Beynen and Katan, 1985a	6	207	1,596
	6	207	1,596
Oh and Miller, 1985	21	474	654
Edington et al., 1987	33	120	188
	135	120	188
McNamara et al., 1987	39	192	628
	36	288	575
Kestin et al., 1989	10	180	686
	15	204	735
Clifton et al., 1990	Normal: 11	185	681
	Hypercholesterolemic diet-insensitive: 22	185	681
	Hypercholesterolemic diet-sensitive: 23	185	681

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
–0.09		
0.05	40	
0.16	38	
0.03	38	
0.49	38	
0.00	38	
0.75	41	
0.62	41	
0.40	40	
1.47	38	0.17
0.48	46	0.5
0.61	46	0.5
0.27	35	0.62
0.13	26	0.8
0.12	35	0.6
0.16	35	1.45
0.13	35	0.27
–0.02	41	0.37
0.04	36	0.85
0.06	29	0.6
0.19	29	0.6
0.36	29	0.6

continued

TABLE 9-3 Continued

Reference	*n*	Baseline Dietary Cholesterol (mg/d)	Added Dietary Cholesterol (mg/d)
Kern, 1994	8	585	2,393
	8	548	2,462
McCombs et al., 1994	12	213	938
	11	197	888
Clifton et al., 1995	67	151	691
	53	208	939
Sutherland et al., 1997	12	349	250
	14	349	250
Romano et al., 1998	10	200	800
	11	200	800

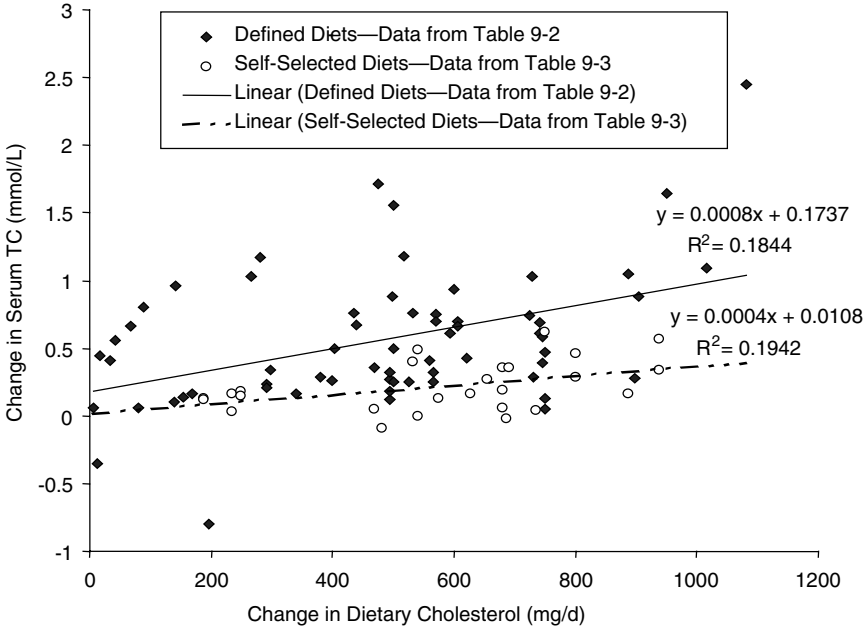

FIGURE 9-1 Relationship between change in dietary cholesterol (0 to 1,000 mg/d) and change in serum total cholesterol (TC) concentration.

Change in Serum Total Cholesterol (mmol/L)	Percent of Calories from Fat	P:S Ratio
0.14	44	0.59
–0.22	44	0.65
0.57	35	0.49
0.16	34	0.54
0.36	35	0.31
0.34	35	0.30
0.18	34	
0.15	34	
0.29	30	
0.46	30	

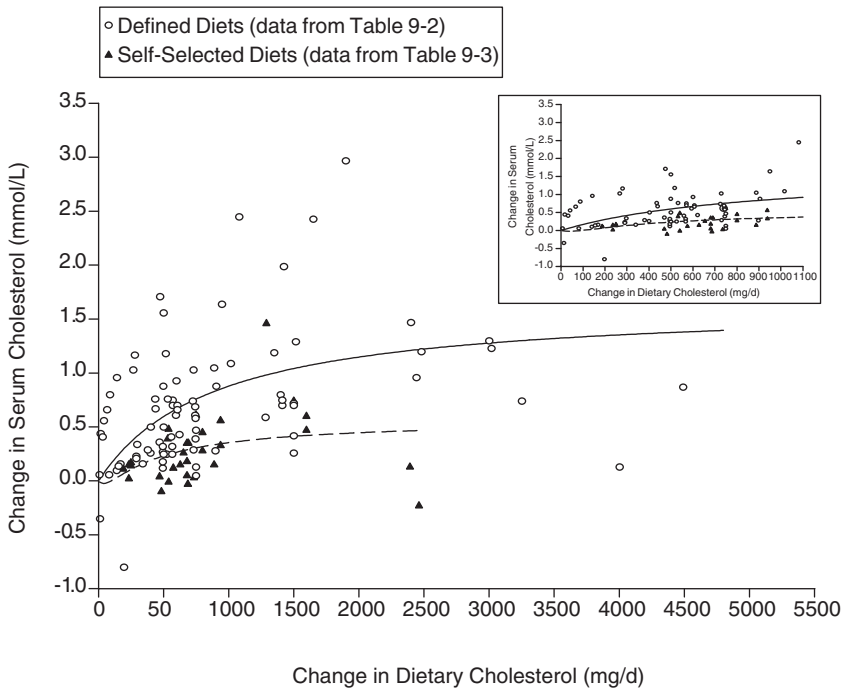

FIGURE 9-2 Relationship between change in dietary cholesterol (0 to 4,500 mg/d) and change in serum cholesterol (TC) concentration.

reported a linear relationship between changes in dietary cholesterol and total serum cholesterol concentration, other studies, including a meta-analysis of 27 controlled metabolic feeding studies of added dietary cholesterol (Hopkins, 1992), have indicated a curvilinear univariate relationship that is quasilinear in the range from 0 to 300 to 400 mg/d of added dietary cholesterol. The range of added dietary cholesterol in the studies was 17 to 4,800 mg/d. The meta-analysis also identified a diminishing increment of serum cholesterol with increasing baseline dietary cholesterol intake. With a baseline cholesterol intake of 0, the estimated increases in serum total cholesterol concentration for intakes from 100 to 400 mg/d of added dietary cholesterol were 0.16 to 0.51 mmol/L, whereas for a baseline cholesterol intake of 300 mg/d, the estimated increases in serum total cholesterol were 0.05 to 0.16 mmol/L (Hopkins, 1992). Another meta-analysis showed that dietary cholesterol raises the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol, therefore adversely affecting the cholesterol profile (Weggemans et al., 2001).

Other predictive formulas for the effect of 100 mg/d of added dietary cholesterol, which did not consider baseline cholesterol intake and are based on compilations of studies with a variety of experimental conditions, have yielded estimates of 0.1 mmol/L (Hegsted, 1986), 0.057 mmol/L (Howell et al., 1997), and 0.065 mmol/L (Clarke et al., 1997), the latter two involving meta-analyses with adjustment for other dietary variables. Furthermore, pooled analyses of the effects of 100 mg/d of added dietary cholesterol on plasma lipoprotein cholesterol concentrations (Clarke et al., 1997) indicated an estimated increase of 0.05 mmol/L in low density lipoprotein (LDL) and 0.01 mmol/L in HDL (ratio of 5 LDL:1 HDL). There is evidence that the increase in HDL is largely accounted for by higher levels of apoE-containing HDL particles (Mahley et al., 1978), but the significance in atherosclerosis protection is not established. Hegsted and coworkers (1993) reported that the majority of the increase in serum total cholesterol concentration with increased cholesterol intake was due to an increase in LDL cholesterol concentration.

The incremental serum cholesterol response to a given amount of dietary cholesterol appears to diminish as baseline serum cholesterol intake increases (Hopkins, 1992). There is also evidence from a number of studies that increases in serum cholesterol concentration due to dietary cholesterol are blunted by diets low in saturated fat, high in polyunsaturated fat, or both (Fielding et al., 1995; National Diet-Heart Study Research Group, 1968; Schonfeld et al., 1982), although this effect has not been observed by others (Kestin et al., 1989; McNamara et al., 1987).

There is considerable evidence for interindividual variation in serum cholesterol response to dietary cholesterol, ranging from 0 to greater than 100 percent (Hopkins, 1992). It has been reported that such responsive-

ness is relatively stable within individuals (Beynen and Katan, 1985b) and appears to be correlated with serum cholesterol response to saturated fatty acids (Katan et al., 1988). Intrinsic differences in intestinal cholesterol absorption (Sehayek et al., 1998), suppression of hepatic cholesterol synthesis by dietary cholesterol (Dietschy et al., 1993; McNamara et al., 1987; Nestel and Poyser, 1976; Quintão et al., 1971), and LDL catabolism (Dietschy et al., 1993; Mistry et al., 1981) may all contribute to the observed variation in dietary cholesterol response.

There is increasing evidence that genetic factors underlie a substantial portion of interindividual variation in response to dietary cholesterol. An instructive case is that of the Tarahumara Indians, who in addition to consuming a diet low in cholesterol, have both low intestinal cholesterol absorption and increased transformation of cholesterol to bile acids (McMurry et al., 1985). However, with an increase in dietary cholesterol from 0 to 905 mg/d, their average plasma cholesterol concentration increased 0.88 mmol/L (from 2.92 to 3.8 mmol/L), the same value predicted by the formula of Hopkins (1992), indicating the likelihood of above-average responsiveness of other aspects of cholesterol or lipoprotein metabolism.

Variations in several genes have been associated with altered responsiveness to dietary cholesterol. The common E4 polymorphism of the apoE gene has been associated with increased cholesterol absorption (Kesäniemi et al., 1987) and with increased plasma LDL cholesterol response to dietary saturated fat and cholesterol in some, but not all studies (Dreon and Krauss, 1997). The recent finding that apoE is of importance in regulating cholesterol absorption and bile acid formation in apoE knockout mice (Sehayek et al., 2000) lends support to a possible role for this gene in modulating dietary cholesterol responsiveness in humans. The A-IV-2 variant allele of the apo A-IV gene has been found to attenuate the plasma cholesterol response to dietary cholesterol (McCombs et al., 1994). Recently, the A-IV-2 allele has been associated with reduced intestinal cholesterol absorption in diets high in polyunsaturated fat but not in diets high in saturated fat (Weinberg et al., 2000). However, this has not been confirmed in other studies (Weggemans et al., 2000). Finally, the recent discovery that defects in the ABCG5 and ABCG8 genes can lead to markedly increased intestinal absorption of both cholesterol and plant sterols (Berge et al., 2000) points to the possibility that more common variants of these genes may contribute to variation in cholesterol absorption and dietary cholesterol response in the general population.

There are numerous other candidate genes that could modulate plasma lipid and lipoprotein response to dietary cholesterol by affecting cholesterol absorption, cellular cholesterol homeostasis, and plasma lipoprotein metabolism. Among the most likely candidates are those regulated

by lipid-responsive nuclear transcription factors, including sterol regulatory element-binding proteins, peroxisome proliferator-activated receptors, and orphan nuclear receptors. Studies in animal models have generated data in support of the possibility that variations among these genes may be of importance in influencing dietary cholesterol response in humans, but to date such human data are lacking. Nevertheless, the existence of marked interindividual variability in dietary cholesterol response among and within various animal models points to the likelihood that some of the mechanisms underlying this variability will also apply to humans.

Cardiovascular Disease and CHD

An association of dietary cholesterol with cardiovascular disease is based on several lines of evidence, including studies in animal models, epidemiological data in humans, and the effects of dietary cholesterol on plasma lipoproteins (Table 9-4). There is compelling evidence that dietary cholesterol can induce atherosclerosis in several animal species, including rabbits, pigs, nonhuman primates, and transgenic mice (Bocan, 1998; McNamara, 2000; Rudel, 1997). However, given the existence of marked inter- and intraspecies differences in cholesterol metabolism and atherogenic mechanisms, it is not possible to extrapolate these data directly to humans.

A number of prospective epidemiological studies have investigated the relationship of dietary cholesterol and other nutrients to the development of coronary heart disease (CHD) (reviewed in Kritchevsky and Kritchevsky, 2000; McNamara, 2000). Significant univariate relationships of cholesterol intake to risk for CHD have been observed in the Seven Countries Study (Kromhout et al., 1995) and the Honolulu Heart Program (McGee et al., 1984). A significant relative risk was also observed in the Western Electric Study, which remained significant after adjustment for a number of covariates, including dietary fat and serum cholesterol concentration (Stamler and Shekelle, 1988). More recently, in a study of 10,802 health-conscious men and women in the United Kingdom, a univariate relationship of cholesterol intake to ischemic heart disease mortality was observed (Mann et al., 1997).

However, a number of other epidemiological studies have not demonstrated a significant independent relationship of dietary cholesterol intake and CHD (Esrey et al., 1996; Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997; Posner et al., 1991). In a cohort of 43,757 male health professionals, dietary cholesterol intake was significantly related to age-adjusted risk for myocardial infarction and fatal CHD ($p < 0.003$ and 0.002, respectively) across cholesterol quintiles ranging from median intakes of 189 to 422 mg/d (Ascherio et al., 1996). However, the risk was

attenuated with multivariate analyses ($p < 0.07$ and 0.03), which included other risk factors such as body mass index, smoking habits, alcohol consumption, physical activity, history of hypertension or high blood cholesterol, family history of myocardial infarction, and profession. The risk became insignificant after adjustment for fiber intake, which was reported to be significantly inversely related to CHD risk in this cohort. A similar cohort analysis in a group of 80,082 female nurses showed a positive but nonsignificant relationship between dietary cholesterol and CHD in quintiles of median intakes ranging from 132 to 273 mg/1,000 kcal/d (Hu et al., 1997). In both the male Health Professionals Follow-up Study and the female Nurses' Health Study cohorts, there was no relationship of egg intake to CHD risk with intakes of up to 1 egg/d (Hu et al., 1999). There was, however, a significant increase of CHD risk associated with higher ranges of egg consumption in patients with diabetes. This finding was corroborated in a European study, but after multivariate analysis adjusting for fiber intake, the association was no longer significant (Toeller et al., 1999).

Measures of atherosclerosis using imaging techniques have also been assessed in relation to diet. Angiographically assessed coronary artery disease progression over 39 months in 50 men was weakly related to cholesterol intake in univariate, but not multivariate, analysis (Watts et al., 1994). In 13,148 male and female participants in the Atherosclerosis Risk in Communities Study, carotid artery wall thickness, an index of early atherosclerosis, was significantly related to dietary cholesterol intake by univariate analyses; multivariate analysis was not performed (Tell et al., 1994).

The lack of consistency in observations relating dietary cholesterol intake to clinical cardiovascular disease and CHD endpoints may be due to many factors, including the limited ability to detect such effects (e.g., due to relatively small increases in LDL cholesterol concentration and inaccuracies in dietary intake data) and to the limited ability to distinguish the effects of dietary cholesterol independent of energy intake and other dietary variables that may be positively (e.g., saturated fat intake) or negatively (e.g., fiber intake) associated with dietary cholesterol and heart disease risk. Another uncertainty relates to interpreting the effects of dietary cholesterol on blood cholesterol concentrations. Evidence indicates that increased dietary cholesterol results, on average, in increased blood concentrations of both LDL and HDL cholesterol, and it is possible that the net impact on cardiovascular disease risk depends on the relative changes in these lipoproteins, as well as on other unmeasured mediators of atherogenesis. Finally, the considerable interindividual variation in lipid response to dietary cholesterol may result in differing outcomes in different populations or population subgroups.

TABLE 9-4 Dietary Cholesterol and Coronary Heart Disease (CHD)

Reference	Study Design	Diet Information
Kromhout and de Lezenne Coulander, 1984	Men, 40–59 y 14 cases 857 controls Cohort, 10-y follow-up	Dietary history
McGee et al., 1984	456 cases 6,632 controls Cohort, 10-y follow-up	24-h recall Adjusted for age
Kushi et al., 1985	Men 110 cases 891 controls Cohort, 20-y follow-up	Dietary history Adjusted for age and cohort
McGee et al., 1985	8,006 men Cohort, 10-y follow-up	24-h recall Adjusted for age
Posner et al., 1991	Men 45–55 y Cohort, 16-y follow-up	24-h recall Multivariate analysis
Tzonou et al., 1993	Men and women 329 cases 570 controls Case-control	Dietary history
Tell et al., 1994	Men and women, 45–64 y Cohort	Food frequency questionnaire
Watts et al., 1994	50 men 26 lipid-lowering diet 24 usual care Intervention	Dietary history

Results[a]	Comments
Mean cholesterol intake (mg/1,000 kcal) Cases 145 Controls 143	No association between cholesterol intake and CHD
Mean cholesterol intake (mg/1,000 kcal) Cases 256 Controls 241	Significant positive association between cholesterol intake and incidence of CHD
Mean cholesterol intake (mg/1,000 kcal) Cases 266 Controls 248	Significantly greater cholesterol intake in CHD deaths
Cholesterol intake (mg/1,000 kcal) / Rate of CHD death (per 1,000) < 125 ≈ 8 125–175 ≈ 16 175–225 ≈ 14 225–275 ≈ 12 275–325 ≈ 13 > 325 ≈ 20	Cholesterol intake as mg/1,000 kcal positively associated with CHD death, but not when intake measured as mg/d
Cholesterol intake (mg/d) / RR of CHD 300 1.0 529 0.99	No association between cholesterol intake and risk of CHD
Mean cholesterol intake (mg/d) Men / Women Cases 345 / 322 Controls 350 / 292	No association between cholesterol intake and CHD
	Cholesterol intake was positively associated with carotid artery wall thickness
Mean cholesterol intake (mg/d) Diet 215 Usual 341	Cholesterol was positively associated with progression of coronary artery disease

continued

TABLE 9-4 Continued

Reference	Study Design	Diet Information
Ascherio et al., 1996	Men 40–75 y 734 cases Cohort, 6-y follow-up	Food frequency questionnaire Multivariate analysis (including fiber intake)
Esrey et al., 1996	52 cases, 30–59 y 3,873 controls 40 cases, 60–79 y 581 controls Cohort, 12-y follow-up	24-h recall Multivariate analysis
Hu et al., 1997	80,082 women, 34–59 y Cohort, 14-y follow-up	Food frequency questionnaire Multivariate analysis
Mann et al., 1997	Men and women, 16–79 y Prospective observation	Food frequency questionnaire Adjusted for age, sex, smoking, and social class
Pietinen et al., 1997	Smoking men, 50–69 y Cohort, 6.1-y follow-up	Food frequency questionnaire Multivariate analysis

Results[a]			Comments
Mean cholesterol intake (mg/d)		RR for MI or fatal CHD	No significant association between cholesterol intake and risk for MI or fatal CHD after adjustment for fiber intake
189		1.00	
246		0.86	
290		0.98	
338		0.94	
422		1.03	
Mean cholesterol intake (mg/d)			Cholesterol intake was not significantly associated with CHD mortality
Age (y)	30–59	60–79	
Cases	427	423	
Controls	416	355	
Quintile of cholesterol intake		RR of CHD	A positive but nonsignificant association between cholesterol intake and risk of CHD
1		1.00	
2		1.19	
3		1.14	
4		1.32	
5		1.25	
Tertile of cholesterol intake		IHD death rate ratio	Increased IHD mortality with increased cholesterol intake
1st		100	
2nd		181	
3rd		353	
Median cholesterol intake (mg/d)		RR of coronary death	No association between cholesterol intake and risk of coronary death
390		1.00	
477		0.90	
543		0.81	
621		0.86	
768		0.92	

continued

TABLE 9-4 Continued

Reference	Study Design	Diet Information
Hu et al., 1999	37,851 men, 40–75 y 866 cases Cohort, 8-y follow-up 80,082 women, 34–59 y 939 cases Cohort, 14-y follow-up	Food frequency questionnaire Multivariate analysis
Toeller et al., 1999	Diabetic men and women, 14–61 y Cross-sectional	3-d dietary records Multivariate analysis (including fiber intake)

[a] RR = relative risk, MI = myocardial infarction, IHD = ischemic heart disease, OR = odds ratio, CVD = cardiovascular disease.

Cancer

As shown in Tables 9-5 through 9-8, no consistent significant associations have been established between dietary cholesterol intake and cancer, including lung, breast, colon, and prostate. Several case-control studies have suggested that a high consumption of cholesterol may be associated with an increased risk of lung cancer (Alavanja et al., 1993; Byers et al., 1987; Goodman et al., 1988; Hinds et al., 1983; Jain et al., 1990). This positive association was shown in one cohort study (Shekelle et al., 1991), but not in three others (Heilbrun et al., 1984; Knekt et al., 1991; Wu et al., 1994).

Dose–Response Assessment

The main adverse effect of dietary cholesterol is increased serum LDL cholesterol concentration, which would be predicted to result in increased risk for CHD. Serum HDL concentration also increases, although to a

Results[a]			Comments
Egg intake (eggs/wk)	Mean cholesterol intake (mg/d)	RR of CHD	No significant association between egg consumption (up to 1 egg/d) and risk of CHD
Men			
< 1	237	1.00	
1	266	1.06	
2–4	330	1.12	
5–6	404	0.90	
≥ 7	536	1.08	
Women			
< 1	228	1.00	
1	258	0.82	
2–4	342	0.99	
5–6	436	0.95	
≥ 7	557	0.82	
Cholesterol intake (mg/d)	OR for CVD		No significant association between cholesterol intake and CVD risk after adjusting for fiber intake
15–236	1.00		
236–335	0.80		
335–461	0.86		
462–2,165	0.96		

lesser extent, but the impact of such a diet-induced change in CHD risk is uncertain.

As reviewed above, on average, an increase of 100 mg/d of dietary cholesterol is predicted to result in a 0.05 to 0.1 mmol/L increase in total serum cholesterol, of which approximately 80 percent is in the LDL fraction. This effect of added cholesterol is highly variable among individuals and is considerably attenuated at higher baseline cholesterol intakes. The LDL cholesterol concentration increase would predict approximately a 1 to 2 percent increase in CHD, with possibly offsetting effects of increased HDL cholesterol concentration. Epidemiological studies have limited power to detect effects of such magnitude and thus do not provide a meaningful basis for establishing adverse effects of dietary cholesterol. Therefore, it would seem reasonable to define the lowest-observed-adverse-effect level for dietary cholesterol as the lowest level shown to increase total or LDL cholesterol concentration. However, no studies have examined the effects of very small increments of dietary cholesterol in numbers of subjects sufficiently large enough to permit statistical treatment of the data. An increase

TABLE 9-5 Dietary Cholesterol and Risk of Lung Cancer

Reference	Study Design	Dietary and Other Information
Hinds et al., 1983	Men 188 cases 294 controls Case-control	Dietary history Adjusted for smoking, age, ethnicity, and occupational exposure
Heilbrun et al., 1984	Men 109 cases 7,420 controls Cohort, 15-y follow-up	24-h recall Adjusted for age and smoking
Byers et al., 1987	Men and women 450 cases 902 controls Case-control	Food frequency questionnaire Adjusted for age and smoking
Goodman et al., 1988	Men and women 336 cases 865 controls Case-control	Dietary history Adjusted for age, ethnicity, and pack-years of smoking
Jain et al., 1990	Men and women 839 cases 772 controls Case-control	Dietary history Adjusted for cumulative cigarette smoking
Knekt et al., 1991	Men 117 cases 4,421 controls Cohort, 20-y follow-up	Dietary history Adjusted for age, smoking, and energy intake

Results[a]			Comments
Cholesterol intake (mg/d)	RR of lung cancer		Increased lung cancer risk was positively associated with cholesterol intake
0–143	1.00		
144–285	1.65		
286–500	2.28		
≥ 501	3.50		
Cholesterol intake (mg/d)	RR of lung cancer		No significant association between lung cancer risk and cholesterol intake
0–299	1.00		
300–499	0.71		
500–749	0.99		
≥ 750	0.98		
Quartile of	RR of lung cancer		Weak but nonsignificant association between cholesterol intake and lung cancer risk in men, but not in women
cholesterol intake	Men	Women	
1 (low)	0.7	1.1	
2	0.9	1.7	
3	1.2	1.2	
4 (high)	1.0	1.0	
Mean cholesterol			Significant positive association between lung cancer risk and cholesterol intake in men, but not in women
intake (mg/d)	Men	Women	
Cases	385	249	
Controls	332	245	
Quartile of	OR for lung cancer		
cholesterol intake	Men	Women	
1 (low)	1.0	1.0	
2	2.3	0.6	
3	1.8	1.5	
4 (high)	2.2	0.9	
Cholesterol intake (mg/d)	OR for lung cancer		Significant increase in risk of lung cancer in highest quartile with cholesterol intake > 468 mg/d
< 235	1.00		
235–342	0.87		
343–468	0.99		
> 468	1.58		
Cholesterol intake (mg/d)	RR of lung cancer		Cholesterol intake was not associated with risk of lung cancer
< 441	1.00		
441–609	0.80		
> 609	1.03		

continued

TABLE 9-5 Continued

Reference	Study Design	Dietary and Other Information
Shekelle et al., 1991	Men 57 cases 1,821 controls Cohort, 24-y follow-up	Dietary history Adjusted for age, smoking, β-carotene intake, and percent of calories from fat
Alavanja et al., 1993	Women 429 cases 1,021 controls All nonsmokers Case-control	Food frequency questionnaire, Multivariate analysis
Wu et al., 1994	Women 212 cases Cohort, 6-y follow-up	Food frequency questionnaire Adjusted for age, smoking, occupation, physical activity, and total energy intake
Swanson et al., 1997	Women 587 cases 624 controls Case-control	Food frequency questionnaire Multivariate analysis

[a] RR = relative risk, M = men, W = women, OR = odds ratio.

in serum cholesterol concentration was observed with as little as 17 mg/d of cholesterol added to a cholesterol-free diet, but only three subjects were studied (Wells and Bronte-Stewart, 1963).

Serum cholesterol concentrations increase with increased dietary cholesterol (Figures 9-1 and 9-2), and the relationship of serum cholesterol concentration to CHD risk or mortality increases progressively (Neaton and Wentworth, 1992; Sorkin et al., 1992; Stamler et al., 1986; Weijenberg et al., 1996). Therefore, it is not appropriate to set a Tolerable Upper Intake Level (UL) for dietary cholesterol because increased risk may occur at a very low intake level and at a level that is exceeded by usual diets.

Results[a]		Comments
Cholesterol intake (mg/d)	RR of lung cancer	Cholesterol intake (specific to consumption of eggs) was positively associated with risk of lung cancer
198–604	1.00	
605–794	1.30	
795–1,909	1.94	
Cholesterol intake (mg/d)	OR for lung cancer	No significant association between cholesterol intake and risk of lung cancer
< 120	1.00	
120–162	0.63	
163–214	0.71	
215–302	1.14	
> 302	1.09	
Quartile of cholesterol intake	RR of lung cancer	Cholesterol intake was not associated with risk of lung cancer
1 (low)	1.0	
2	0.6	
3	0.9	
4 (high)	0.9	
Cholesterol intake (mg/1,000 kcal)	RR of lung cancer	Cholesterol intake was not associated with risk of lung cancer
< 102	1.00	
102–126	1.21	
127–148	0.88	
149–176	1.04	
> 176	1.22	

RISK CHARACTERIZATION

Intakes above an identified Tolerable Upper Intake Level (UL) indicate a potential risk of an adverse health effect. There is much evidence to indicate a positive linear trend between cholesterol intake and low density lipoprotein cholesterol concentration, and therefore increased risk of coronary heart disease (CHD). A UL is not set for cholesterol because any incremental increase in cholesterol intake increases CHD risk. Because cholesterol is unavoidable in ordinary, nonvegan diets, eliminating cholesterol in the diet would require significant changes in patterns of dietary intake. Such significant adjustments may introduce undesirable effects (e.g., inadequate intakes of protein and certain micronutrients) and unknown and unquantifiable health risks. Nonetheless, it is possible to

TABLE 9-6 Dietary Cholesterol and Risk of Breast Cancer

Reference	Study Design	Dietary and Other Information
Hirohata et al., 1987	Caucasian women 161 cases 161 hospital controls 161 neighborhood controls Case-control	Dietary history
Jones et al., 1987	Women 99 cases 5,386 controls Cohort, mean 10-y follow-up	24-h recall Multivariate analysis
Willett et al., 1987	Women 601 cases Cohort, 6-y follow-up	Food frequency questionnaire Multivariate analysis
van den Brandt et al., 1993	Women 55–69 y Cohort, 3.3-y follow-up	Food frequency questionnaire Multivariate analysis
Franceschi et al., 1996	Women 2,569 cases 2,588 controls Case-control	Food frequency questionnaire Multivariate analysis

[a] RR = relative risk, OR = odds ratio.

have a diet low in cholesterol while consuming a nutritionally adequate diet. Dietary guidance for minimizing cholesterol intake is provided in Chapter 11.

RESEARCH RECOMMENDATIONS

- Studies are needed to identify possible mechanisms whereby early nutritional experiences, such as dietary cholesterol, affect the atherosclerotic

Results[a]		Comments
Mean cholesterol intake (mg/d)		No significant differences in cholesterol intake between breast cancer cases and controls
Cases	286	
Controls	267–289	
Cholesterol intake (mg/d)	RR of breast cancer	No association between cholesterol intake and risk of breast cancer
< 130	1.00	
130–233	1.33	
233–415	0.79	
> 415	0.70	
Mean cholesterol intake (mg/d)	RR of breast cancer	No association between cholesterol intake and breast cancer
204	1.00	
262	1.06	
325	1.02	
345	1.07	
436	0.91	
Quintile of cholesterol intake	RR of breast cancer	No association between cholesterol intake and risk of breast cancer
1	1.00	
2	0.84	
3	0.85	
4	0.85	
5	1.09	
Cholesterol intake (mg/d)	OR for breast cancer	No association between cholesterol intake and risk of breast cancer
< 224	1.00	
225–281	0.93	
282–335	0.90	
336–414	0.97	
> 414	0.91	

process in adults and the sensitive periods in development when this may occur.

- The molecular mechanisms that regulate absorption of dietary cholesterol need to be determined.
- Specific genetic variants that contribute to wide interindividual variation in low density lipoprotein (LDL) cholesterol response to dietary cholesterol need to be delineated.

TABLE 9-7 Dietary Cholesterol and Risk of Colon Cancer

Reference	Study Design	Dietary and Other Information
Willett et al., 1990	Women Cohort, 6-y follow-up	Food frequency questionnaire Adjusted for age and total energy intake
Sandler et al., 1993	Men and women 236 cases 409 controls Case-control	Food frequency questionnaire Adjusted for age, alcohol intake, body mass index, and calories
Giovannucci et al., 1994	Men 205 cases Cohort, 6-y follow-up	Food frequency questionnaire Adjusted for age and total energy intake
Le Marchand et al., 1997	698 male case-control pairs 494 female case-control pairs Case-control	Food frequency questionnaire Multivariate analysis
Pietinen et al., 1999	Male smokers Cohort, 8-y follow-up	Food frequency questionnaire Multivariate analysis

[a] RR = relative risk, OR = odds ratio.

Results[a]			Comments
Cholesterol intake (mg/d)	RR of colon cancer		Increased risk of colon cancer associated with cholesterol intake > 406 mg/d
< 247	1.00		
247–299	1.09		
300–344	0.75		
345–406	1.07		
> 406	1.39		
Cholesterol intake (mg/d)	OR for colorectal adenomas		No association between cholesterol intake and risk of colorectal adenomas
< 156	1.0		
156–189	0.78		
190–227	0.73		
228–289	0.89		
> 289	0.99		
Quintile/median cholesterol intake (mg/d)	RR of colon cancer		No association between cholesterol intake and risk of colon cancer
1/198	1.0		
2/262	1.27		
3/313	0.99		
4/369	1.07		
5/467	1.07		
Quartile of cholesterol intake from eggs	OR for colorectal cancer		Cholesterol intake (limited to cholesterol from eggs) was positively associated with risk of colorectal cancer
	Men	Women	
1 (low)	1.0	1.0	
2	1.8	1.3	
3	1.8	1.5	
4 (high)	2.0	2.0	
Quartile/median cholesterol intake (mg/d)	RR of colorectal cancer		No association between cholesterol intake and risk of colorectal cancer
1/378	1.0		
2/501	1.2		
3/594	1.1		
4/759	1.0		

TABLE 9-8 Dietary Cholesterol and Risk of Prostate Cancer

Reference	Study Design	Dietary and Other Information
Kolonel et al., 1988	452 cases 899 controls Case-control	Dietary history Adjusted for age and ethnicity
Andersson et al., 1996	522 cases 536 controls Case-control	Food frequency questionnaire Adjusted for age and energy
Key et al., 1997	328 cases 328 controls Case-control	Food frequency questionnaire
Vlajinac et al., 1997	101 cases 202 controls Case-control	Dietary history Adjusted for energy and significant nutrients

[a] OR = odds ratio.

- Other factors (dietary and constitutional) that contribute to the wide interindividual variation in LDL cholesterol response to dietary cholesterol also need to be delineated.
- Studies are needed to better define the relation between dietary cholesterol intakes and LDL cholesterol concentrations over a broad range of cholesterol intakes, from very low to high.
- The relationship between dietary cholesterol intakes and body pools of cholesterol needs to be determined.

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Results[a]			Comments
	Age and OR for		Significant positive
Quartile of cholesterol	prostate cancer		association between
intake	≤ 70	≧ 70	cholesterol intake and
1 (low)	1.0	1.0	risk of prostate cancer,
2	1.2	1.6	but no clear gradient
3	1.2	1.7	effect
4 (high)	1.3	1.6	
Cholesterol intake (mg/d)	OR for prostate cancer		No association between
< 241	1.00		cholesterol intake and
241–301	0.71		risk of prostate cancer
302–390	0.85		
> 390	0.96		
Mean cholesterol intake			No significant difference
(mg/d)			in cholesterol intake
Cases 341			between prostate
Controls 351			cancer cases andcontrols
Tertile of cholesterol intake	OR for prostate cancer		No significant association
1	1.00		between cholesterol
2	0.97		intake and risk of
3	0.60		prostate cancer

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