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Review

Hypertension, serum lipids and cancer risk: A review of epidemiological evidence

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ABSTRACT

Although the association between blood pressure, serum lipids and cancer risk has been investigated, the results are controversial. The aim of this literature review was to examine the epidemiological evidence and provide overview of the association between blood pressure, serum lipids and cancer risk. The arterial hypertension is closely linked with renal cell cancer development. Risk of renal cell cancer was 2–4 times higher for persons with arterial hypertension, independently of sex. In some studies arterial hypertension as one of the components of the metabolic syndrome, was associated with a higher risk of colorectal, prostate cancer and malignant melanoma. Studies suggest that a higher total serum cholesterol level is linked with higher risk of colorectum, colon, prostate and testicular cancer and lower risk of stomach, liver and hematopoietic and lymphoid tissues cancer. There was positive association between serum triglycerides and esophageal, colorectal, lung, renal, thyroid cancer. Given that hypertension is a common risk factor worldwide and its control remains inadequate, our analysis supports the relevance of public health programs aimed at reducing hypertension to reduce the incidence of a number of cancers including renal cell cancer. Effective cholesterol control may lower the risk of cancer, but further studies with longer follow-up and repeated measurements of cholesterol and other lipids are needed.

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1. Introduction

Arterial hypertension (AH) and plasma lipid profile levels (low high-density lipoprotein (HDL) and/or raised triglyceride (TG)) are among other acknowledged key risk factors for atherosclerosis and coronary heart disease. Changes in lifestyle factors including unhealthy diet, harmful use of alcohol, lack of physical activity, excess weight and aging of population determined the increased prevalence of chronic conditions such as high blood pressure and high blood cholesterol worldwide [1,2]. In 2008, worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension [1]; the global prevalence of elevated plasma cholesterol levels among adults was 39% (37% for males and 40% for females) [3]. The influence of blood pressure and cholesterol on cancer risk has been an area of investigation for long-time. Many studies and meta-analyses had separately reported these factors as important etiologic factors for the development and progression of certain types of cancer.

The aim of this literature review was to examine the epidemiologic evidence and provide overview of the association between blood pressure, serum lipids and cancer risk.

2. Association between arterial hypertension and cancer

2.1. *Kidney cancer*

Arterial hypertension (AH) is the most important modifiable risk factor for cardiovascular, cerebrovascular and renal disease. Epidemiological evidence shows that there are several factors which play an important role in the development, evolution and prognosis of AH, some of them non-modifiable, such as age, sex, ethnicity and heredity, and others modifiable, such as body weight, salt intake, alcohol intake, use of hormonal contraceptives and drugs retaining sodium, sedentary life and psychosocial factors [4,5]. There is increasing evidence that AH affects the potential for the development of kidney cancer. Worldwide, kidney cancer is the 13th most common malignancy, with approximately 271,000 new cases diagnosed in 2008, and renal cell carcinoma (RCC) accounts for about 90%–95% of them [6]. The Czech Republic, Lithuania, Latvia, Estonia, and Iceland have the highest RCC rates in Europe. An increase in RCC incidence has been observed globally during the last decades, although in some European countries RCC incidence is declining in recent years [6]. Tumor causes are varied, but it is established that smokers as well as overweight and obese patients have increased risk [6]. Many cohort [5–12] and case–control [13] studies linked RCC with a history of AH (Table 1).

In Sweden 363,992 men were investigated in a cohort study, 759 persons with RCC were identified. RCC risk increased with increasing systolic and diastolic blood pressure and severity of AH [7]. The risk of RCC was more than two-fold higher for men who had increased diastolic blood pressure of 90 mm Hg or more compared to below 70 mm Hg. Relative risk of developing kidney cancer was 60%–70% higher in men with systolic blood pressure of 150 mm Hg or more than those <120 mm Hg.

European Prospective Investigation into Cancer and Nutrition (EPIC) study of 296,638 men and women recruited in 1992–1998 investigated the relation between blood pressure, antihypertensive medication, and RCC [10]. Renal cancer was diagnosed for 250 subjects during the study period. The researchers found that increased arterial blood pressure is associated with an increased risk of RCC development independently of sex, body mass index, smoking and use of antihypertensive medication. Furthermore, the risk of RCC was higher in men, whose blood pressure rose by more than 14 mm Hg during the six year period as compared to men whose blood pressure changed less. A reduced risk was observed in those whose blood pressure decreased during 6 years.

In 2002–2007, Colt and colleagues studied the incidence of AH and kidney cancer links in Detroit and Chicago (USA) cities depending on the race using a case–control study methodology. Kidney cancer was diagnosed in 843 whites and 358 blacks during the period of the study, the controls were 707 whites and 519 blacks. The study results showed that AH increased the chance for kidney cancer development 2 times (95% CI, 1.7–2.5), 1.9 times in whites, and 2.8 times in blacks. The kidney cancer risk increased with a longer duration of AH. After 25 years of tracking it reached 4.1 times in blacks and 2.6 times in whites. The possibility of developing kidney cancer was even greater for individuals with poor AH control [13]. It is possible that a high incidence of kidney cancer in Lithuania among men and women [6] could be due to a high prevalence of AH that is poorly treated [24].

A combined analysis of the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) cohorts in the United States examined AH, use of diuretics, BMI, change of weight and smoking as independent RCC risk factors in a prospective study, which included 48,953 men and 118,191 women working in the health care system. The study results showed that the relative risk to suffer from kidney cancer in men and women with AH was 1.8 (95% CI, 1.2–2.7) and 1.9 (95% CI, 1.4–2.7) times higher, respectively. No increased risk to suffer from RCC in men taking thiazide diuretics had been determined [5]. Other researchers also identified a significant direct relationship between AH and RCC development [9,12,25]. The issue of whether use of diuretics and antihypertensive drugs is also associated with an increased risk of kidney cancer development remains unresolved, although some studies suggest that antihypertensive treatment may not be a risk factor as long as blood pressure is effectively controlled [4,5,7,10,26,27]. Despite the high correlation between obesity, AH and RCC risk, these factors have been shown as independent of each other risk factors. The risk to suffer from kidney cancer is higher among those who are obese and have AH than those who have one of these risk factors [7,10]. The US Multiethnic Cohort study estimated that more than 15% of RCC in male cases and 24% of RCC in female cases could be attributed to hypertension [8]. However, the biological mechanism of relationship between the AH and kidney cancer is still not clear, association with chronic renal hypoxia and lipid peroxidation formation of reactive oxygen cultivars has been linked to tumor development and might be partly responsible for the increased RCC risk [28,29].

Table 1 – Risk estimates of incident cancer by site for blood pressure.

Study	Study population (*n*)	Risk estimates (95% CI)[a]	*P* for trend[c]
Cohort studies			
Colorectum (C18–C21)			
Stocks et al. [14]	578,700	SBP: 1.26 (1.00–1.59) in men	0.004
		0.79 (0.55–1.10) in women	0.17
		DBP: 1.42 (1.08–1.82) in men	0.001
		1.00 (0.71–1.42) in women	0.88
Pancreas (C25)			
Johansen et al. [15]	577,315	Mid-BP: 1.39 (1.04–1.85) in men	0.06
		1.94 (1.24–3.00) in women	0.01
Malignant melanoma (C43)			
Stocks et al. [11]	577,799	Mid-BP: 1.96 (1.29–2.97) in men	0.003
Nagel et al. [16]	578,700	Mid-BP: 2.02 (1.33–3.07) in men	0.125
		1.19 (0.76–1.87) in women	0.421
		1.37 (0.87–2.25) in women	0.06
Endometrium (C54)			
Bjørge et al. [17]	288,834 women	SBP: 1.38 (1.07–1.77)	0.003
		DBP: 1.11 (0.88–1.39)	0.2
Prostate (C61)			
Stocks et al. [18]	336,159	SBP: 0.84 (0.76–0.91)	<0.0001
		DBP: 0.82 (0.76–0.90)	0.3
Häggström et al. [19]	289,866 men	SBP: 0.95 (0.81–1.12)	0.440
		DBP: 1.06 (0.87–1.28)	0.857
Kidney (C64)			
Flaherty et al. [5]	167,144	1.9 (1.4–2.7)[b] for women	NA
		1.8 (1.2–2.7)[b] for men	
Chow et al. [7]	363,992 men	SBP: 1.7 (1.1–2.6) in men	<0.001
		DBP: 2.2 (1.1–4.5) in men	<0.001
Setiawan et al. [8]	161,126	1.58 (1.09–2.28)[b] for women	NA
		1.42 (1.07–1.87)[b] for men	
Vatten et al. [9]	72,416	SBP: 1.0 (0.5–1.9) in men	0.59
		2.0 (0.9–4.6) in women	0.11
		DBP: 0.9 (0.4–2.0) in men	0.49
		1.6 (0.8–3.5) in women	0.13
Weikert et al. [10]	296,638	SBP: 2.48 (1.53–4.02)	<0.001
		DBP: 2.34 (1.54–3.55)	0.003
Stocks et al. [11]	577,799	Mid-BP: 3.62 (2.09–6.28) in men	<0.001
		0.86 (0.40–1.85) in women	0.6
Häggström et al. [12]	560,388	SBP: 3.40 (1.91–6.06) in men	<0.001
		1.06 (0.43–2.62) in women	0.54
		DBP: 3.33 (1.85–5.99) in men	<0.001
		1.58 (0.60–4.14) in women	0.41
Bladder (C67)			
Häggström et al. [20]	578,700	SBP: 1.31 (0.95–1.80) in men	0.02
		1.12 (0.48–2.60) in women	0.94
		DBP: 1.29 (0.90–1.85) in men	0.03
		0.81 (0.37–1.81) in women	0.85
Brain (C71)			
Edlinger et al. [21]	578,462	SBP: 1.45 (1.01–2.09)	NA
		DBP: 1.84 (1.24–2.72)	NA
Lymph/hematopoietic tissue (C85–C96)			
Nagel et al. [16]	575,386	Mid-BP: 0.94 (0.70–1.26) in men	0.934
		1.07 (0.72–1.59) in women	0.837
All cancers (C00–C96)			
Stocks et al. [11]	577,799	SBP: 1.22 (1.12–1.34) in men	<0.001
		1.08 (0.96–1.21) in women	<0.001
		DBP 1.27 (1.16–1.40) in men	0.07
		1.07 (0.95–1.20) in women	0.1
Case–control studies			
Colorectum (C18–C21)			
Pelucchi et al. [22]	2256 cases, 4661 controls	AH: 1.24 (1.03–1.48) in men[b]	NA
		AH: 0.87 (0.71–1.06) in women[b]	
Colon (C18)			
Pelucchi et al. [22]	1378 cases, 4661 controls	AH: 1.36 (1.10–1.68) in men[b]	NA
		AH: 0.92 (0.73–1.16) in women[b]	

Table 1 (*Continued*)

Study	Study population (*n*)	Risk estimates (95% CI)[a]	*P* for trend[c]
Rectum (C19–C21)			
Pelucchi et al. [22]	878 cases, 4661 controls	AH: 1.08 (0.84–1.40) in men[b] AH: 0.80 (0.59–1.07) in women[b]	NA
Prostate (C61)			
Pelucchi et al. [23]	1294 cases, 1451 controls	AH: 1.14 (0.96–1.36)[b]	NA
Kidney (C64)			
Colt et al. [13]	1217 cases, 1235 controls	AH: 2.0 (1.7–2.5)[b]	NA

SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); mid-BP, mid-blood pressure (SBP + DBP)/2; AH, hypertension; NA, not available.

[a] The highest versus the lowest level of blood pressure, if otherwise not indicated.

[b] Hypertension, yes versus no.

[c] Test for linear trend.

2.2. *Prostate cancer*

The multicenter case–control study and meta-analysis investigated the relationship between metabolic syndrome and prostate cancer risk [23,30]. It was determined that the AH as one of the metabolic syndrome component increased the risk of prostate cancer by approximately 15%. The researchers concluded that although the hypertension as individual component of metabolic syndrome did not significantly increase the risk of prostate cancer, the combination of three or more components of metabolic syndrome increased the risk of developing prostate cancer significantly up to 4 times [23]. The cohort study conducted in Sweden, in which 336,159 men working in construction were examined and followed-up for on average 22.2 years, showed the opposite trend. Comparing the highest quintile with the lowest one in both systolic and diastolic blood pressure the identified relative risk of prostate cancer was approximately 15%–20% lower ($P < 0.0001$ for systolic and $P = 0.3$ for diastolic trend), the suggestive positive link between blood pressure and a higher mortality was found. The authors could not explain what reasons could lead to a reduction in the risk of prostate cancer incidence [18]. Similarly, Häggström et al. found no significant association between elevated blood pressure and prostate cancer incidence, but positive association with an increased risk of death from prostate cancer was observed: RR top versus bottom quintile of systolic blood pressure was 1.62 (95% CI, 1.07–2.45) [19].

2.3. *Colon and rectal cancer*

Elevated blood pressure or AH has been linked to increased risks of colon and colorectal cancer in large European studies. In a multicenter case–control study, which took place in Italy and Switzerland the relation between metabolic syndrome and colorectal cancer in men was assessed. This study analyzed 1378 cases of histologically confirmed colon cancer, 878 cases of rectal cancer and 4661 controls. AH being one of the metabolic syndrome components significantly increased the chance of colorectal cancer development in men, OR 1.24 (95% CI, 1.03–1.48) compared with those who had no AH [23]. Results of this case–control study are in agreement with the Metabolic syndrome and Cancer project (Me-Can) cohort study a significant association with blood pressure was observed in men (RR 1.10; 95% CI, 1.02–1.18) [14].

2.4. *Other cancer sites*

The results from several large prospective studies suggest that elevated blood pressure may be associated with an increased risk of incident and fatal malignant melanoma [11,16], bladder [20], pancreatic [15], endometrial [17], brain [21] and several other cancer types [11,16,21]. Further research is necessary to understand the possible pathways between hypertension and cancer.

3. Association between dyslipidemias and cancer

It has been shown that elevated serum cholesterol is one of the most important coronary heart disease risk factors. Cholesterol accumulation in the bloodstream can cause atherosclerotic plaques to form within artery walls. In recent years high serum cholesterol has been linked to the development of cancer although the results are inconsistent (Table 2). Several underlying mechanisms by which cholesterol and carcinogenesis may be linked have been proposed. Lipids are the major cell membrane components essential for various biological functions including cell growth and division for the maintenance of cell integrity. Cholesterol is a precursor of bile acids and steroid hormones, it may cause increased tumor angiogenesis, reduced tumor apoptosis and increased tumor cell proliferation [46]. One of the proposed mechanisms involves a vital role of cholesterol in cell membranes, which could affect various signaling pathways [47] and relevant proteins like the cell survival kinase Akt [48].

Different association between cholesterol and cancer risk among men and women, sites of cancer, populations and lipids profile was reported in a number of epidemiologic studies. Several studies have reported an inverse relationship between serum total cholesterol levels and cancer risk [31,33,41,42,49], whereas some found a positive association [34,50]. A prospective Korean cohort study found that a high total cholesterol level (≥240 mg/dL) was positively related to the prostate, colon cancer in men and breast cancer in women, but negatively associated with risk of liver, stomach cancer in both men and women, and lung cancer in men [33]. Inverse relationships were also found for cancers of the liver/intrahepatic bile duct, pancreas, non-melanoma of skin and lymph/hematopoietic tissue among men and for gallbladder,

Table 2 – Relative risk of incident cancer by site for total serum cholesterol (TC), low density lipoprotein (LDL) and triglyceride (TG).

Study	Study population (*n*)	Risk estimates[a] and 95% CI	*P* for trend[e]
Cohort studies			
Esophagus (C15)			
Strohmaier et al. [31]	577,330	TC: 1.12 (0.59–2.12) in men	0.79
		TC: 1.51 (0.26–8.83) in women	0.35
Wulaningsih et al. [32]	540,309	TG: 2.29 (1.42–3.68)	0.0001
Stomach (C16)			
Strohmaier et al. [31]	577,330	TC: 0.71 (0.50–1.01) in men	0.14
		TC: 0.84 (0.50–1.42) in women	0.72
Kitahara et al. [33]	78,419	TC: 0.87 (0.82–0.93) in men	<0.001
		TC: 0.86 (0.77–0.97) in women	0.06
Iso et al. [34]	33,368	TC: 1.29 (0.95–1.75) in men[d]	0.0002
		TC: 0.84 (0.47–1.51) in women[d]	0.67
Asano et al. [35]	2604	TC: 1.62 (0.86–3.06)[b]	0.02
Ulmer et al. [36]	156,153	TC: 1.45 (0.97–2.17)	0.208
Colorectum (C18–C21)			
Stocks et al. [11]	578,700	TC: 1.22 (1.00–1.47) in men	0.009
		TC: 1.42 (1.09–1.85) in women	0.004
		TG: 1.65 (1.27–2.13) in men	0.001
		TG: 1.16 (0.85–1.62) in women	0.015
Colon (C18)			
Strohmaier et al. [31]	577,330	TC: 1.18 (0.92–1.51) in men	<0.01
		TC: 1.23 (0.90–1.69) in women	0.15
Kitahara et al. [33]	53,944 men	TC: 1.12 (1.00–1.25)	0.05
Ulmer et al. [36]	156,153	TG: 1.08 (0.81–1.43)	0.547
Wulaningsih et al. [32]	540,309	TG: 1.30 (1.12–1.52)	<0.0001
Rectum (C19–C21)			
Strohmaier et al. [31]	577,330	TC: 1.09 (0.81–1.48) in men	0.92
		TC: 1.48 (0.94–2.32) in women	0.49
Ulmer et al. [36]	156,153	TG: 1.56 (1.00–2.44)	0.184
Wulaningsih et al. [32]	540,309	TC: 1.32 (1.09–1.59)	0.0003
Liver (C22)			
Strohmaier et al. [31]	577,330	TC: 0.14 (0.07–0.29) in men	<0.01
		TC: 0.96 (0.22–4.07) in women	0.24
Kitahara et al. [33]	78,419	TC: 0.42 (0.38–0.45) in men	<0.01
		TC: 0.32 (0.27–0.39) in women	<0.001
Iso et al. [34]	33,368	TC: 2.62 (1.44–4.76) in men[d]	<0.0001
		TC: 4.15 (1.70–10.15) in women[d]	0.0003
Gallbladder (C23)			
Strohmaier et al. [31]	577,330	TC: 1.27 (0.44–3.69) in men	0.80
		TC: 0.23 (0.08–0.62) in women	<0.01
Pancreas (C25)			
Strohmaier et al. [31]	577,330	TC: 0.52 (0.33–0.81) in men	0.01
		TC: 1.08 (0.60–1.97) in women	0.44
Ulmer et al. [36]	156,153	TG: 1.19 (0.70–2.05)	0.188
Lung (C33–C34)			
Strohmaier et al. [31]	577,330	TC: 1.15 (0.95–1.40) in men	0.22
		TC: 1.24 (0.88–1.76) in women	0.05
Kitahara et al. [33]	53,944 men	TC: 0.89 (0.82–0.96)	<0.001
Ulmer et al. [36]	156,153	TG: 1.94 (1.47–2.54)	<0.0001
Breast (C50)			
Strohmaier et al. [31]	288,057 women	TC: 0.70 (0.61–0.81)	<0.01
Kitahara et al. [33]	24,475 women	TC: 1.17 (1.03–1.33)	0.03
Iso et al. [34]	21,685 women	TC: 0.87 (0.50–1.53)[d]	0.90
Ulmer et al. [36]	84,460 women	TC: 0.95 (0.70–1.28) for ≤50 years	0.455
		TC: 1.05 (0.79–1.39) for >50 years	0.352
Cervical (C53)			
Iso et al. [34]	21,685 women	TC: 0.61 (0.17–2.17)[d]	0.47
Ulmer et al. [36]	84,460 women	TC: 2.00 (0.89–4.50)	0.038
Endometrium (C54)			
Ulmer et al. [36]	84,460 women	TC: 1.61 (0.97–2.67)	0.206
Ovarian (C56)			
Ulmer et al. [36]	84,460 women	TC: 1.43 (0.71–2.85)	0.576
Prostate (C61)			
Häggström et al. [19]	289,866 men	TC: 0.96 (0.85–1.10)	0.711

Table 2 (*Continued*)

Study	Study population (*n*)	Risk estimates[a] and 95% CI	*P* for trend[e]
		TG: 0.88 (0.74–1.04)	0.001
Strohmaier et al., 2013 [31]	289,273 men	TC: 0.99 (0.88–1.13)	0.86
Iso et al., 2009 [34]	11,683 men	TC: 0.43 (0.23–0.82)[d]	0.0013
Mondul et al., 2010 [37]	6816 men	TC: 1.22 (1.03–1.44)	0.01
Platz et al., 2009 [38]	5586 men	TC: 0.41 (0.22–0.77)[b]	0.01
Ulmer et al., 2009 [36]	71,693 men	TG: 0.67 (0.56–0.80)	<0.001
Shafique et al., 2012 [39]	12,926 men	TC: 2.28 (1.27–4.10) (Gleason sc. ≥8)[a]	n.a.
Testicular (C62)			
Wiréhn et al. [40]	44,864 men	TC: 4.5 (1.3–16.2)	0.005
Kidney (C64)			
Häggström et al. [12]	560,388	TC: 1.15 (0.74–1.78) in men	0.83
		TC: 1.56 (0.77–3.17) in women	0.11
		TG: 1.79 (1.00–3.21) in men	0.01
		TG: 1.04 (0.41–2.66) in women	0.56
Strohmaier et al. [31]	577,330	TC: 1.06 (0.71–1.58) in men	0.94
		TC: 1.13 (0.61–2.07) in women	0.40
Ulmer et al. [36]	156,153	TC: 1.27 (0.81–1.97)	0.105
Bladder (C67)			
Häggström et al. [20]	578,700	TC: 1.08 (0.83–1.40) in men	0.93
		TC: 0.92 (0.50–1.67) in women	0.80
		TG: 1.20 (0.85–1.70) in men	0.36
		TG: 0.62 (0.30–1.31) in women	0.55
Thyroid (C73)			
Strohmaier et al. [31]	577,330	TC: 0.64 (0.25–1.62) in men	0.4
		TC: 0.85 (0.56–1.30) in women	0.31
Ulmer et al. [36]	156,153	TG: 1.96 (1.00–3.84)	0.492
Lymph/hematopoietic tissue (C85–C96)			
Benn et al. [41]	70,179	LDL: 1.42 (0.55–3.67)[b]	<0.001
Strohmaier et al. [31]	577,330	TC: 0.68 (0.54–0.87) in men	0.02
		TC: 0.61 (0.44–0.83) in women	0.01
Ulmer et al., 2009 [36]	156,153	TG: 0.68 (0.43–1.07) (for NHL)	0.033
All cancer (C00–C96)			
Strasak et al. [42]	172,210	TC: 0.58 (0.43–0.78) in men	<0.0001
		TC: 0.69 (0.49–0.99) in women	0.03
Benn et al. [41]	70,179	LDL: 1.41 (1.14–1.76)[b]	<0.001
Strohmaier et al. [31]	577,330	TC: 0.94 (0.88–1.00) in men	0.11
		TC: 0.86 (0.79–0.93) in women	<0.01
Kitahara et al. [33]	78,419	TC: 0.84 (0.81–0.86) in men	<0.001
		TC: 0.91 (0.8–0.95) in women	<0.001
Iso et al. [34]	33,368	TC: 1.20 (1.02–1.41) in men[d]	0.0045
		TC: 1.07 (0.85–1.34) in women[d]	0.91
Borena et al. [43]	257,585 men	TG: 1.16 (1.06–1.26) in men[a]	0.001
	256,512 women	TG: 1.15 (1.05–1.27) in women[a]	0.003
Case–control studies			
Colorectum (C18–C21)			
Pelucchi et al. [22]	2256 cases, 4661 controls	TC: 1.14 (0.93–1.40) in men[c]	n.a.
		TC: 0.83 (0.66–1.03) in women[c]	
Chung et al. [44]	105 cases, 105 controls	TC: 0.2 (0.1–0.6)	n.a.
		TG: 0.3 (0.1–0.8)	
Colon (C18)			
Pelucchi et al. [22]	1378 cases, 4661 controls	TC: 1.27 (1.00–1.61) in men[c]	n.a.
		TC: 0.91 (0.70–1.18) in women[c]	
Rectum (C19–21)			
Pelucchi et al. [22]	878 cases, 4661 controls	TC: 0.97 (0.72–1.31) in men[c]	n.a.
		TC: 0.69 (0.49–0.98) in women[c]	
Prostate (C61)			
Pelucchi et al. [23]	1294 cases, 1451 controls	TC: 1.54 (1.26–1.89)[c]	
Platz et al. [45]	698 cases, 698 controls	TC: 0.61 (0.39–0.98)[b]	0.13

[a] Total serum cholesterol, highest compared to the lowest level if otherwise not indicated.
[b] Lowest compared to the highest.
[c] Hypercholesterolemia, yes compared to no.
[d] <4.14 compared to 4.65–5.16 mmol/L.
[e] Test for linear trend.

breast, melanoma of skin and lymph/hematopoietic tissue among women in the Me-Can project study [31].

Epidemiologic studies suggest that cancer risk is higher for persons who have high serum low-density lipoprotein (LDL) cholesterol levels [41] or TG [43] levels. In contrast, other studies found an inverse relationship between serum TG and stomach cancer [35] or oral cancer [51]. The short-term inverse association with cancer and no significant association after longer time from baseline measurements of total serum cholesterol or high-density lipoproteins (HDL) [42,52] or the U-shaped relationship between the TG levels and cancer incidence [53,54] are observed. Strasak et al. provided data obtained from a 19-year prospective study of 172,210 healthy adults conducted in Austria [42]. There were short-term decreased risks of the overall, digestive organs, lymphatic and hematopoietic tissue cancer in the highest total serum cholesterol tertile compared with the lowest tertile. However, such relationship was not observed after 5, 12 and 24 months from diagnosis.

3.1. *Stomach cancer*

The Japan Public Health Center-based prospective study (JPHC) on 33,368 men and women did not show a sustained association between the total serum cholesterol level and total cancer or major cancer types, although the inverse relationship between the total serum cholesterol level and stomach cancer and liver cancer was identified regardless the hepatitis C virus infection and alcohol consumption habits [34]. A similar inverse relationship between serum cholesterol levels and gastric cancer has been observed in another Japanese cohort study of 2604 men and women [35]. Taking into account *Helicobacter pylori* infection, atrophic gastritis, hemoglobin A1c level, and leukocyte count, family history of malignant tumors, body mass index, smoking habits, and diet, the results showed the inverse relationship between stomach cancer and cholesterol levels in serum: the risk of stomach cancer increased with decreasing blood cholesterol levels. In this study, serum cholesterol especially affected the incidence of intestinal-type gastric cancer. Researchers concluded that a low level of blood cholesterol is an independent factor for stomach cancer (particularly intestinal type) development.

3.2. *Prostate cancer*

There is no consensus of opinion about cholesterol levels and prostate cancer link. Several studies have explored a positive association between cholesterol and prostate cancer [22,33,34,37,38]. Meanwhile, others revealed either an inverse relationship [36] or no association [19,31] between high serum total cholesterol levels and prostate cancer. Health Professionals Follow-Up Study and Prostate Cancer Prevention Trial explored the relationship between cholesterol levels and incidence of prostate cancer, type of this cancer, stage and differentiation degree [38,45]. The results showed that a low serum cholesterol level is associated with a lower risk of a high-grade and advanced disease. In these studies, there was no established link with the overall incidence of prostate cancer and a lower degree of differentiation of prostate tumor. The Japanese JPHC study demonstrated a strong positive association between total cholesterol levels and risk of advanced prostate cancer [34]. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland found inverse associations between both total and HDL and prostate cancer which were attenuated when the first 10 years of follow-up were excluded; this study also found a positive association between total cholesterol and advanced prostate cancer [47]. The findings from the UK population-based cohort study also showed that men with higher cholesterol are at greater risk of developing high-grade prostate cancer but not overall risk of prostate cancer [39]. These results supported the hypothesis that blood cholesterol status influenced growth and progression of prostate cancer.

3.3. *Breast cancer*

Increasing evidence demonstrates the role of lipoproteins in the development and progression of breast cancer [55]. Llaverias et al. showed that increased plasma cholesterol, in association with oncogenic stimuli, lead to accelerate the development of breast cancer and exacerbates their aggressiveness [56]. Furthermore, it has been observed that plasma cholesterol levels were reduced during breast tumor development but not prior to its initiation. A recent meta-analysis by Esposito et al. included nine studies to investigate the association between metabolic syndrome and postmenopausal breast cancer. The meta-analysis showed risk estimation of 1.39 ($P = 0.008$) in patients with lower high-density lipoprotein cholesterol values while there was no association between TG values and postmenopausal breast cancer [57].

3.4. *Other cancer sites*

A number of studies analyze relationship between total cholesterol levels and increased risk of colon and rectal cancer, results are ambiguous. Evidence from prospective Me-Can [14] and Swedish AMORIS [32] studies support an association between high total serum cholesterol levels and colorectal cancer risk. In contrast to these data, a case–control study in Korea showed that serum total cholesterol and TG levels were significantly associated with a reduced colorectal cancer risk [44]. A large population-based cohort study in Sweden indicate that subjects with the total serum cholesterol level of ≥7.0 mmol/L had a 4.5 times higher risk of developing testicular cancer [40], thus suggesting a relationship between high concentration of cholesterol and risk of testicular cancer.

The relationship between types of serum lipids and oral cancer, premalignant disease and their relationship with tobacco smoking were analyzed in prospective case–control longitudinal study [51]. The results showed the inverse relationship between serum lipids and oral cancer: patients with oral cancer were found to have significantly reduced total serum cholesterol, TG, HDL cholesterol and very LDL levels. It has been identified that serum lipid levels did not differ between smokers and non-smokers groups.

There is no consensus if LDL cholesterol levels influence the incidence of cancer. The strong correlation between low LDL cholesterol levels and increased cancer risk was revealed in a Copenhagen population study [41]. This study demonstrated that subjects with a LDL cholesterol level lower than

87 mg/dl had a 43% higher risk of developing cancer, compared to persons with higher than 158 mg/dL. Shor et al. found increased risk of hematopoietic cancer in study participants with low serum LDL cholesterol levels (≤70 mg/dL) [58]. Another previous study reported an inverse relationship between LDL levels and hematological tumors. The results showed that LDL cholesterol levels reverted to normal in tumor remission [59]. In Chinese patients with type 2 diabetes mellitus who were not receiving statin therapy, a V-shaped association between a LDL cholesterol level and cancer risk was detected. The study found that LDL cholesterol levels below 2.80 mmol/L and levels at least 3.80 mmol/L were both associated with an increased risk of cancer among patients who did not use statins [54]. The population-based case–control study in Changhai found that high serum levels of TG (≥160 mg/dL) and low levels of HDL (<30 mg/dL) were significantly associated with excess risks of biliary tract cancers [53]. Investigation in Austria revealed that higher TG concentration is associated with approximately 2-fold higher thyroid cancer risk [36].

Eichholzer et al. found a link between low serum cholesterol concentration (i.e. <5.16 mmol/L) and increasing both the overall mortality from cancer and mortality risk from prostate, colon and lung cancer among men over 60 year of age [60]. A similar inverse association for cancer mortality was reported from the Japanese cohort study. Researchers observed that mortality from cancer was higher in the group of subjects with a low cholesterol level (<4.14 mmol/L) comparing to subjects who had an average serum total serum cholesterol level (4.14–5.17 mmol/L) [49]. Meanwhile, a high total serum cholesterol level (≥6.21 mmol/L) had no link with mortality. It has been suggested that the observed negative relationship is likely attributable to an effect of preclinical cancer or disease on cholesterol levels rather than reflecting a true causal relationship [61]. The preclinical cancer effect has been tested after the exclusion of cancer cases occurring during the first few years of follow-up [60]. However, the relative risk estimates for lung cancer, colon, prostate, and overall cancer mortality remained significantly higher for a low serum cholesterol level (<5.16 mmol/L). Another explanation for the inverse cancer mortality–cholesterol relationship is that subjects with high total serum cholesterol are more likely to be censored due to cardiovascular deaths before developing cancer [62]. Nevertheless, other authors suggested that some etiologic role for total serum cholesterol cannot be ruled out [31]. Colli et al. showed the inverse relationship between a high total serum cholesterol level and mortality from prostate cancer for time periods when statin use was high (46% or greater) but not low in the United States, indicating that cholesterol-lowering drugs might have reduced mortality from prostate cancer [63].

4. Conclusions

This analysis supports the hypothesis that individuals with hypertension, both women and men, have an increased risk of kidney cancer. High blood pressure also appears to increase the risk of other types of cancer. More research, is needed to clarify the association between hypertension and risk of cancer of colorectum, prostate, malignant melanoma and brain. Considering the issue of serum cholesterol and the risk of specific cancer sites, some studies showed a negative association with stomach, liver cancer, and a positive association with colorectal, high-grade prostate, and testis cancers but no clear association with pancreas, breast, and low grade prostate cancers. Low HDL was also associated with increased risk of lung, breast, prostate cancer and non-Hodgkin's lymphoma. Low serum cholesterol, however, may be a consequence, rather than a cause, of the neoplastic process (i.e. reverse causation). From a public health perspective these results are important because hypertension is highly prevalent in many developed countries and its control remains inadequate. Relevant public health efforts aimed at preventing and effectively controlling hypertension to reduce the incidence of a number of diseases including kidney cancer are necessary.

Conflict of interest

The authors state no conflict of interest.

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