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RESEARCH PAPER

Dietary Cholesterol and Risk of Cancer: A Multi-site Case-Control Study in Uruguay

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Abstract. The scientific evidence has inconsistencies regarding the relationship between dietary cholesterol and risk of cancer. The present study aimed to assess the odds ratios (ORs) of eleven cancer sites in relation to intake of dietary cholesterol. In the time period 1996-2004, 3,539 patients with several cancer sites (oral cavity and pharynx, esophagus, stomach, colon, rectum, larynx, lung, female breast, prostate, urinary bladder, kidney) and 2,032 hospitalized controls were interviewed using a structured questionnaire by two trained social workers. Dietary cholesterol was estimated through a local table of chemical composition of foods. ORs for these cancer sites were calculated through polytomous (multinomial) multiple regression. Dietary cholesterol was positively associated with the risk of colon, lung, breast, prostate, and urinary bladder cancer and inversely associated with gastric cancer, with the highest OR being observed for bladder cancer (OR 2.57, 95% CI 1.57-4.21). Cancers of the oral cavity, pharynx, larynx, esophagus, rectum and kidney were not significantly associated with risk. The present study adds to the evidence that dietary cholesterol could be a risk factor for several cancer sites, suggesting that lowering the intake of red meat, processed meat, and eggs could be a useful step in the prevention of certain cancers.

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1. Introduction

Dietary cholesterol is found only in foods of animal origin, such as meat, eggs, cheese, milk and butter [1-2]. The first monograph by the World Cancer Research Fund/American Institute of Cancer Research [1] has reported evidence of a relationship between a high cholesterol intake and an increased risk of lung cancer, pancreas, and endometrium, and no evidence of breast cancer risk.

Furthermore, several case-control and prospective studies have suggested evidence of positive association [3-7] between high intake of dietary cholesterol and cancers of the lung, colorectum, pancreas, and kidney. On the other hand, other studies found a lack of association between dietary cholesterol and cancers of the stomach, lung, ovaries and pancreas [8-15]. Therefore the effect of alimentary cholesterol on cancer is conflictive. Recently, Hu et al. [16] reported increased risks of several cancers and dietary cholesterol in the framework of a large population-based multisite case-control study conducted in Canada.

It should be emphasized that most of these studies were performed in developed countries and there is lack of evidence of association between dietary cholesterol intake and several cancer sites in developing countries. Uruguay, being a developing country, is the major producer of beef (a major source of food cholesterol) in the world [17]. For this reason we decided to conduct a new study on dietary cholesterol and risk of eleven cancer sites in a high-risk country like Uruguay.

2. Patients and Methods

2.1. Selection of cases

In the time period 1996-2004 a multisite case-control study, jointly designed by the Epidemiology Group of the School of Medicine of Uruguay and the International Agency for Research on Cancer (IARC), recruited all the newly diagnosed and microscopically confirmed cases which occurred in the four major public health hospitals of Montevideo. In brief, cancers of the oral cavity, pharynx, esophagus, stomach, colon, rectum, larynx, lung, female breast, prostate, urinary bladder, and kidney (only renal cell carcinoma) were considered eligible for the study. A total number of 3,744 patients were identified and 205 patients refused the interview, leaving a final number of 3,539 cases (response rate 94.5%).

2.2. Selection of controls

In the same time period and in the same hospitals all hospitalized patients with non-neoplastic conditions not related to smoking and drinking and without recent changes in their diets were considered eligible for the study. A initial number of 2,117 patients were approached and 85 of them refused the interview, leaving a final total number of 2,032 patients (response rate 96.0%). These patients were included as controls and they presented the following conditions: eye disorders (437 patients, 21.5%), abdominal hernia (420, 20.7%), fractures (240, 11.8%), injuries (148, 7.3%), varicose veins (145, 7.1%), diseases of the skin (143, 7.0%), urinary stones (142, 6.9%), acute appendicitis (111, 5.5%), hydatid cyst (107, 5.3%), blood disorders (65, 3.2%), osteoarticular disorders (42, 2.1%), and genital diseases (32, 1.6%).

2.3. Interviews and questionnaire

All the participants (cases and controls) were face-to-face interviewed by two trained social workers shortly after hospitalization. Proxy interviews were not allowed. The interviewers administered a structured questionnaire which included the following sections: sociodemographics (age, residence, education, income), a complete occupational history based in the last four jobs and its duration, family history of cancer among the first-degree relatives, self-reported weight and height five

TABLE 1. Frequency of participants by cancer site.

Cancer site	Nº males	Nº females	Nº total	%
Oral cavity and pharynx	274	9	283	8.0
Esophagus	184	50	234	6.6
Stomach	191	84	275	7.8
Colon	87	89	176	5.0
Rectum	127	58	185	5.2
Larynx	274	7	281	7.9
Lung	876	55	931	26.3
Breast	-	461	461	13.0
Prostate	345	-	345	9.7
Bladder	224	30	254	7.2
Kidney	77	37	114	3.2
Total cases	2659	880	3539	100.0
Total controls	1346	686	2032	100.0

TABLE 2. Mean values for age, education, body mass index, smoking and drinking, stratified by cancer site for both sexes.

Site	Age[1]	Education[2]	BMI[3]	Smoking[4]	Drinking[5]
Oral cavity and pharynx	59.8	4.3	23.4	27.6	213.1
Esophagus	66.2	3.5	24.5	22.6	123.7
Stomach	65.5	3.9	25.3	16.0	85.4
Colon	64.3	4.5	25.8	13.7	45.7
Rectum	66.2	4.4	25.5	14.8	70.3
Larynx	62.1	4.1	24.3	32.6	194.0
Lung	62.0	4.2	24.7	31.6	135.9
Breast	59.7	5.3	27.3	4.0	12.1
Prostate	70.6	3.7	26.0	18.0	96.4
Bladder	66.9	4.4	25.6	19.3	84.0
Kidney	60.6	4.7	26.5	15.6	78.0
All cases	63.5	4.3	25.3	21.5	108.5
All controls	62.3	4.5	25.9	13.5	75.3

[1] Age in years
[2] Education in years
[3] Body mass index (weight/height^1.5).
[4] Number of cigarettes/day.
[5] Ml ethanol per day.

years before the date of the interview, a complete smoking history (age of start, age of quit, number of cigarettes smoked per day, type of tobacco, type of cigarette, inhalation practices), a complete drinking history (age of start, age of quit, number of glasses drunk per day, types of alcoholic beverages), a complete history of non-alcoholic beverages (maté, coffee, tea, soft drinks), menstrual and reproductive events, and a food frequency questionnaire on 64 items. This FFQ was considered representative of the Uruguayan diet and allowed the estimation of total energy intake. Furthermore, the FFQ was tested for reproducibility with good results [18].

2.4. Estimation of nutrients

Thirty-five nutrients, including cholesterol, were estimated using a local table of chemical composition of foods [19]. Dietary cholesterol was energy-adjusted using the residuals method of Willett and Stampfer [20-21].

TABLE 3. Mean intake of dietary cholesterol by cancer sites and controls.

Dietary cholesterol (mg/day)			
Cancer site	**Men**	**Women**	**Both sexes**
Oral cavity and pharynx	556.3	351.1	549.8
Esophagus	522.6	455.7	508.3
Stomach	496.0	436.9	477.9
Colon	512.0	483.0	497.4
Rectum	526.6	441.4	499.9
Larynx	556.6	440.3	553.7
Lung	535.9	527.7	535.4
Breast	-	467.7	467.7
Prostate	469.2	-	469.2
Bladder	518.7	544.3	521.7
Kidney	484.4	333.8	435.5
All cases	523.5	463.2	508.5
All controls	450.9	426.1	442.5

TABLE 4. Number of cases for cancer sites and number of controls.

Dietary cholesterol (mg/day)				
Cancer site	**<=334**	**335-443**	**444-572**	**573+**
Oral cavity and pharynx	37	70	69	107
Esophagus	43	60	62	69
Stomach	45	70	90	70
Colon	37	41	41	57
Rectum	30	51	44	60
Larynx	41	49	76	115
Lung	146	204	235	346
Breast	97	124	122	118
Prostate	79	86	69	111
Bladder	48	62	52	92
Kidney	31	28	23	32
All cases	634	845	883	1177
All controls	508	508	508	508

2.5. Statistical analysis

Relative risks, approximated by the odds ratios, were estimated by multiple polytomous regression [22]. We compared the results with those obtained using unconditional multiple logistic regression [22] and the results were very similar. We fitted the following model: age (continuous), sex (categorical), residence (categorical, 3 strata), education (categorical, 3 strata), income (categorical, 3 strata), body mass index (continuous), smoking index (categorical, 8 strata including smoking status, smoking cessation and number of cigarettes smoked per day among current smokers), age of start smoking (continuous), alcohol drinking (categorical, 5 strata), maté consumption (categorical, 4 strata), total energy intake (continuous), total vegetables and fruits (continuous), saturated fat (continuous), and dietary cholesterol (categorical, 4 strata). Test of trend was calculated entering categorical variables as continuous. All the calculations were performed using the software STATA (release 10) [23].

3. Results

The frequency of cases and controls is shown in TABLE 1. The most frequent site was cancer of

TABLE 5. Odds ratios of cancer sites for dietary cholesterol.[1,2]

Dietary cholesterol (mg/day)				
	335-443	444-572	573+	
Cancer site	**OR 95% CI**	**OR 95% CI**	**OR 95% CI**	***P* value trend**
UADT[3]	0.92 0.68-1.26	0.78 0.57-1.07	1.10 0.81-1.48	0.63
Oral cavity and pharynx	0.74 0.50-1.11	0.76 0.51-1.14	1.17 0.80-1.71	0.26
Esophagus	1.12 0.75-1.68	1.11 0.74-1.65	1.06 0.71-1.60	0.81
Stomach	0.88 0.63-1.24	0.71 0.50-1.02	0.55 0.37-0.80	0.001
Colon	1.01 0.62-1.62	1.15 0.72-1.84	1.99 1.29-3.08	0.002
Rectum	1.20 0.77-1.87	1.15 0.73-1.81	1.28 0.82-2.00	0.33
Colorectum	1.12 0.80-1.57	1.17 0.83-1.63	1.65 1.19-2.29	0.003
Larynx	1.18 0.80-1.75	0.85 0.56-1.29	1.07 0.73-1.59	0.86
Lung	1.29 0.98-1.70	1.43 1.09-1.86	1.78 1.38-2.31	<0.0001
Breast	1.22 0.81-1.86	1.60 1.07-2.41	1.99 1.30-3.06	<0.0001
Prostate	1.61 1.09-2.37	2.30 1.57-3.39	2.10 1.43-3.09	<0.0001
Bladder	1.38 0.86-2.24	2.22 1.37-3.60	2.57 1.57-4.21	<0.0001
Kidney	1.17 0.67-2.05	1.22 0.68-2.16	1.51 0.87-2.61	0.15
All cases	1.20 1.02-1.42	1.37 1.16-1.62	1.68 1.42-1.98	<0.0001

[1] Adjusted for age, sex (when necessary), residence, education, income, body mass index, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, age of start smoking, alcohol drinking, maté consumption, total energy intake, total vegetables & fruits intake, and saturated fat.

[2] Reference category: lowest quartile (≤334 mg cholesterol).

[3] Cancer of the upper aerodigestive tract including oral cavity, pharynx, and larynx.

the lung (26.3%), followed by female breast (13.0%), prostate (9.7%), oral cavity and pharynx (8.0%), larynx (7.9%), and stomach (7.8%).

The characteristics of cancer sites and controls are shown in TABLE 2. The highest mean age was observed in prostate cancer (70.6 years), whereas the lowest mean age corresponded to breast cancer (59.7 years). The highest educational level was observed among prostate cancer (5.3 years of education), whereas patients with esophageal cancer showed a low education (3.5 years of education). The highest relative weight was observed among breast cancer (27.3 of body mass index), whereas the lowest BMI was observed among patients with cancer of the oral cavity and pharynx (23.4 of body mass index). The highest mean of cigarettes smoked per day was observed among cases with laryngeal cancer, closely followed by patients with lung cancer (31.6 cigarettes smoked per day), whereas the lowest mean for smoking was observed among colon cancer (13.7 cigarettes smoked per day) and breast cancer (4.0 cigarettes smoked per day). The highest mean for consumption of alcohol (in ml/day of ethanol per day) was observed among patients afflicted with cancer of the oral cavity and pharynx (213 ml/ethanol per day), whereas breast cancer showed a mean of 12.1 of ethanol per day.

The mean consumption of dietary cholesterol is shown in TABLE 3. Among male patients the highest mean intake of cholesterol was observed among those with laryngeal cancer (556.6 mg per day), whereas the lowest mean was presented among prostate cancer patients (469.2 mg per day). Among females, the highest mean intake of dietary cholesterol was showed for lung cancer (527.7 mg per day) and the lowest mean intake was presented by patients with renal cell carcinoma (333.8 mg per day). Among both sexes together, patients with laryngeal cancer showed the highest mean intake (553.7 mg per day) whereas patients with renal cell cancer showed the lowest mean intake of dietary cholesterol (435.5 mg per day).

The number of cases and controls by category is shown in Table 4 and the corresponding odds ratios (and ninety-five percent confidence intervals) are shown in TABLE 5. The ORs for the highest category of

cholesterol intake versus the lowest one were observed for cancers of the colon (OR 1.99, 95% CI 1.29-3.01), colorectum (OR 1.65, 95% CI 1.19-2.29), lung (OR 1.76, 95% CI 1.31-2.28), female breast (OR 1.99, 95% CI 1.30-3.06), prostate (OR 2.10, 95% CI 1.43-3.09), urinary bladder (OR 2.57, 95% CI 1.57-4.21) and all sites together (OR 1.68, 95% CI 1.46-2.04). Cancers of the mouth, pharynx, esophagus, rectum and kidney were not associated with intake of dietary cholesterol. On the other hand, gastric cancer was inversely associated with cholesterol intake (OR 0.55, 95% CI 0.37-0.80).

4. Discussion

This is the first study on dietary cholesterol and risk of eleven cancer sites conducted in a developing country, like Uruguay. Dietary cholesterol was positively associated with elevated risk of cancers of colon, lung, female breast, prostate, and urinary bladder. On the contrary, gastric cancer was inversely associated with cholesterol intake. Finally, oral cavity, pharynx, esophagus, larynx, and kidney cancers were not associated with an increase in the risk of dietary cholesterol.

To our knowledge, this is the first study which explored the relationship between cholesterol from foods and cancers of the upper aerodigestive tract (UADT). High intake of dietary cholesterol was not associated with UADT cancers. These null associations were consistent for oral cavity, pharynx, and larynx cancers.

Similarly esophageal cancer was not associated with dietary cholesterol (p-value for trend = 0.81). On the contrary, a previous study by Mayne et al. [24] showed that a high intake of cholesterol increased the risks for squamous cell and adenocarcinoma of the esophagus.

Gastric cancer was inversely associated with a high intake of dietary cholesterol. However, elevated risks for gastric cancer have been observed among case-control studies conducted in USA, Canada, Mexico and Spain [16,24-26], while a case-control study carried out in Northern Italy reported null results [8]. Thus, the effect of food cholesterol in gastric carcinogenesis is largely unknown and conflictive.

In the present study, alimentary cholesterol was positively associated with colorectal cancer, doubling the risk of this malignancy. Our findings replicate previous prospective and case-control studies [5,16,27-28]. On the contrary, several studies reported null associations between dietary cholesterol and colorectal cancer [29-33]. According to experimental studies, dietary cholesterol could be considered as co-carcinogen, acting in the late-stages of colonic carcinogenesis [34].

Since the pioneer study by Hinds et al. [35] dietary cholesterol has been suggested as a risk factor for lung cancer. A case-control study by Goodman et al. [7] replicated the results of the study by Hinds et al. [35]. Our group conducted a case-control in which fat and cholesterol were considered positively associated with lung cancer [36]. In particular, eggs consumption was strongly associated with small cell carcinoma of the lung [37]. More recently, a pooled study of prospective studies, in which fat and cholesterol were not associated with lung cancer, was conducted by Smith-Warner et al. [15]. Finally, a recent study conducted in Canada reported a high and positive association between dietary cholesterol and lung cancer [16]. All these studies were adjusted for several combinations of tobacco smoking.

Our study showed a high risk of breast cancer for dietary cholesterol, replicating the findings of Hu et al. [16]. On the other hand, several prospective studies reported null findings [38-40]. Recently an experimental study strongly suggested that dietary cholesterol acts in the development and in the progression of breast cancer [41].

The only cancer site which was inversely associated with cholesterol in the Canadian study was prostate cancer [16]. Conversely, our study showed a positive association for this

malignancy of an increased risk of 2.10 (95% CI 1.43-3.09). In fact, our study replicates the findings in the study by Platz et al. [42] suggesting that high serum low density lipoproteins cholesterol (LDL-C) increased the risk of advanced prostate cancer. Our cases corresponded to advanced prostate cancer. Furthermore, in a factor analysis study of advanced prostate cancer [43] the dietary pattern called Western loaded on red meat, processed meat and eggs, and was positively associated with high risk for this malignancy.

Studies on dietary cholesterol and bladder cancer risk are sparse. The study by Riboli et al. [44] focused on saturated fat for which an elevated risk was found, but the study did not found an increased risk for alimentary cholesterol. Hu et al. [16] reported an elevated risk for bladder cancer in a large study conducted in Canada. The findings of our study showed elevated ORs, even higher than those shown in the Canadian study.

In our study, renal cell carcinoma showed an increase in risk of 51% for high intake of cholesterol, which was non-significant. On the other hand, at least two studies reported an increased risk of renal cell cancer positively associated with a high intake of dietary cholesterol [16,45].

Concerning potential mechanisms linking cancer development and cholesterol, an experimental study examined its role in the regulation of tumour progression in a mouse model of mammary tumour formation [41], suggesting that cholesterol accelerates and enhances tumor formation. In addition, tumors were more aggressive, and tumor angiogenesis was enhanced.

Like other case-control studies, the present one has limitations and strengths. The main limitations are related to selection and recall bias. Since cases and controls were similar on sociodemographic characteristics, selection bias appears to be a minor problem. Perhaps recall bias is a major difficulty and could result in differential misclassification. On the other hand, the Uruguayan population is largely unaware of the role of diet in cancer. Also, even the interviewers were not focused on the role of cholesterol in the cancer sites which were studied. In fact, cases and control were drawn from a low educational subpopulation, since admittance to the public health hospitals is restricted to population with low incomes. Perhaps the major strength is related to the high response rate for cases and controls, resulting in a very cooperative subpopulation. Another strength is the microscopic validation of the cases by expert pathologists from the School of Medicine.

In summary, we conducted a multisite case-control study involving eleven cancer sites and dietary cholesterol appears to be a major risk factor for five cancers (colon, lung, female breast, prostate, and urinary bladder). It could be concluded that a diet rich in cholesterol could enhance the risk for these cancer sites.

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