Socioeconomic status and colon cancer incidence: a prospective cohort study

AJM van Loon¹, PA van den Brandt¹ and RA Golbohm^{1,2}

¹Department of Epidemiology, University of Limburg, Maastricht, The Netherlands; ²Department of Nutrition, TNO-Toxicology and Nutrition Institute, Zeist, The Netherlands.

Summary The association between socioeconomic status and colon cancer was investigated in a prospective cohort study that started in 1986 in The Netherlands among 120 852 men and women aged 55-69 years. At baseline, data on socioeconomic status, alcohol consumption and other dietary and non-dietary covariates were collected by means of a self-administered questionnaire. For data analysis a case-cohort approach was used, in which the person-years at risk were estimated using a randomly selected subcohort (1688 men and 1812 women). After 3.3 years of follow-up, 312 incident colon cancer cases were detected: 157 men and 155 women. After adjustment for age, we found a positive association between colon cancer risk and highest level of education (trend P = 0.13) and social standing (trend P = 0.008) for men. Also, male, upper white-collar workers had a higher colon cancer risk than blue-collar workers (RR = 1.42, 95% CI 0.95-2.11). Only the significant association between social standing and colon cancer risk persisted after additional adjustment for other risk factors for colon cancer (trend P = 0.005), but the higher risk was only found in the highest social standing = 2.60, 95% CI 1.31-5.14). In women, there were no clear associations between the socioeconomic status indicators and colon cancer.

Keywords: colon cancer; socioeconomic status; lifestyle; cohort study

Different associations between socioeconomic status (SES) and colon cancer risk have been observed depending on study design. Correlation (Baquet et al., 1991) and crosssectional (Williams and Horm, 1977; Faivre et al., 1989) studies did not show consistent associations, but case-control (Papadimitriou et al., 1984; Ferraroni et al., 1989; Bidoli et al., 1992) and cohort studies (Pukkala and Teppo, 1986; Vågerö and Persson, 1986; Leon, 1988) showed predominantly positive associations between SES and colon cancer risk. In these studies hardly any adjustment was made for potential confounders. Most of the time, age was included in the analyses, and two studies included some lifestyle characteristics such as smoking (Williams and Horm, 1977) and coffee and alcohol consumption (Ferraroni et al., 1989). Although associations have been reported between SES and colon cancer, SES is not thought to be a direct risk factor. Lifestyle variables that have been identified as possible risk factors for colon cancer, e.g. dietary factors such as fat, fibre or energy intake (Freudenheim and Graham, 1989; Willett, 1989), alcohol consumption (Kune and Vitetta, 1992), physical activity (Gerhardsson et al., 1988; Slattery et al., 1988) or reproductive factors (Kravdal et al., 1993), are all characteristics associated with SES (Noppa and Bengtsson, 1980; Baghurst et al., 1990; Jacobsen and Lund, 1990; Hulshof et al., 1991). Therefore we examined the association between SES and colon cancer incidence and the influence of various lifestyle factors such as Quetelet index, alcohol consumption, large bowel cancer in the family, physical activity and reproductive factors (the last for women only) in a prospective cohort study on diet, other lifestyle variables and cancer risk. Earlier research in the cohort study did not show associations between (fresh) meat consumption or fat intake and risk of colon cancer (Goldbohm et al., 1994a). Therefore, these dietary factors were omitted from our analyses.

Materials and methods

The cohort study

In September 1986, The Netherlands Cohort Study (NLCS), investigating various lifestyle variables, sociodemographic indicators and cancer risk, was started. A detailed description of the cohort study design has been reported elsewhere (Van den Brandt et al., 1990a). Briefly, the cohort included 58 279 men and 62 573 women aged 55-69 years at the beginning of the study. The study population originated from 204 municipal population registries throughout the country. Data were collected by means of a self-administered questionnaire. For data analysis the case-cohort approach was used in which cases are derived from the entire cohort, while the personyears at risk are estimated from a random sample of 3500 subjects (subcohort). After the baseline exposure measurement the subcohort was randomly sampled (1688 men and 1812 women) and it has been followed up biennially for vital status information.

Follow-up for incident cancer has been established by record linkage with all regional cancer registries in The Netherlands and with a national pathology register (PALGA). The method of record linkage has been described previously (Van den Brandt et al., 1990b). The analysis is restricted to colon cancer incidence in the period from September 1986 to December 1989. In this period, completeness of follow-up was estimated to be 95% (Van den Brandt et al., 1993). After these 3.3 years of follow-up, 351 colon cancer cases were detected. We excluded self-reported prevalent cancer cases other than skin cancer (n = 28), cases with in situ carcinoma (n = 8), cases without microscopically confirmed diagnosis (n = 2) and sarcoma (n = 1). Therefore 312 incident cases (157 males and 155 females) were available for analysis. Self-reported prevalent cancer cases other than skin cancer were also excluded from the subcohort, with the result that 3346 subjects (1630 men and 1716 women) remained in this group.

Socioeconomic status

SES was measured by means of highest level of education attained and by means of occupational history, two of the

Correspondence: AJM van Loon, University of Limburg, Department of Epidemiology, POB 616, 6200 MD Maastricht, The Netherlands

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recommended measures for SES (Liberatos et al., 1988). Educational level of the individual and his or her partner was classified as primary school, lower vocational school (e.g. technical school, domestic science school), junior high school, senior high school, higher vocational school, university and other education. Information about occupational history was coded according to a job coding system of the Central Bureau of Statistics (CBS) frequently used in The Netherlands (Centraal Bureau voor de Statistiek, 1985). For the present analysis, these CBS codes were aggregated according to occupational sector and required training (EGP) and according to social standing (U&S). The EGP coding scheme is a reconstruction of the scheme developed by Erikson et al. (1979), which is still comparable with the original list (Ganzeboom et al., 1987). The U&S score is based on an ordering of occupational titles according to social standing and is also comparable with international classifications (Van Berkel-van Schaik and Tax, 1990). Other factors relevant to the association between SES and colon cancer risk that were measured are Quetelet index (kg m⁻²), alcohol intake, large bowel cancer in the family, physical activity during work and the prevalence of cholecystectomy. For women parity and age at first birth were also measured.

Data analysis

The distribution of SES indicators and potential confounders known to be associated with SES and colon cancer were compared between the case and subcohort group, for men and women separately. Educational level was aggregated into five categories: primary school, lower vocational school, junior high school, senior high school and higher vocational school or university. The EGP score of the last occupation was divided into four categories: blue-collar jobs (lowergrade technicians, semi- and unskilled manual workers), lower white-collar jobs (administrators and non-manual employees), upper white-collar jobs (professionals) and other (farmers, self-employed people and housewives). The U&S score (also based on the last occupation) was divided into five categories increasing from low (e.g. garbage collector) to high social standing (e.g lawyers); for women an extra category for housewives was added. The associations between SES and covariates were also studied in the subcohort, by comparing mean values of age, Quetelet index, alcohol intake, parity and mean age at first birth and comparing the prevalence of cholecystectomy, large bowel cancer in the family and high physical activity at work in relevant SES categories.

To study the association between SES and colon cancer risk and the role of possible confounders, data were analysed according to the case-cohort approach (Self and Prentice, 1988; Van den Brandt *et al.*, 1993), using the GLIM statistical package (Baker, 1985). Mantel-Haenszel rate ratios of colon cancer were determined for each of the SES indicators, stratified for age. In the multivariate analyses, rate ratios and 95% confidence intervals of colon cancer were computed for the different SES indicators, after adjustment for the covariates mentioned above. The analyses were conducted for men and women separately.

Results

The distribution of SES indicators and covariates in the group of cases and the subcohort is presented in Table I. Cases were on average older than members of the subcohort (mean age for cases is 62.7 and for subcohort members 61.4), the mean alcohol intake was higher among cases and a history of large bowel cancer in the family and cholecystectomy was also more prevalent in the case groups. High physical activity at work was somewhat more prevalent among cases. Female colon cancer cases had a lower mean number of children and a higher mean age at first birth. The association between the different SES indicators and colon cancer incidence is consistent in men; in the case group there were more men with a higher level of education, a white-collar job and a high U&S score (social standing) compared with the subcohort. For women there was hardly any differ-

Table I	Distribution	of SES	indicators a	and	potential	confounders	in	colon	cancer	cases	and	subcohort,	for	men	and	women
						separately	,									

		separate	Iy						
			len			men			
	Subo	cohort	С	ases	Subo	cohort	Cases		
Characteristics	n	%	n	%	n	%	n	%	
Total	1630		157		1716		155		
Age (mean years ± s.d.)		4 ± 4.2	62	.9 ± 4.2		5 ± 4.3	62.	6 ± 4.0	
Quetelet index (mean kg m ⁻² \pm s.d.)	25.	0 ± 2.7	25	.3 ± 2.9	25.	2 ± 3.5	24.	5 ± 3.6	
Alcohol intake (mean g day ⁻¹ ±s.d.)	14.	5 ± 16.5	16	.0 ± 17.7	5.	8 ± 9.6	6.	4 ± 10.6	
Parity ^a (mean \pm s.d.)					2.	5 ± 2.7	2.	1 ± 2.7	
Age at first birth ^{a,b} (mean±s.d.)						8 ± 4.2	27.	3 ± 4.2	
Cholecystectomy (yes)	74	4.6	12	7.6	229	13.6	31	20.0	
Large bowel cancer in family (yes)	84	5.2	10	6.4	91	5.3	14	9.0	
Physical activity at work ^c (high)	267	20.7	32	23.5	252	22.7	25	25.3	
Highest level of education									
Primary school	458	28.4	38	24.5	603	35.8	54	35.3	
Lower vocational	338	20.9	33	21.3	384	22.8	33	21.6	
Junior high school	420	26.0	35	22.6	476	28.2	42	27.5	
Senior high school	123	7.6	19	12.3	86	5.1	8	5.2	
Higher vocational/university	275	17.0	30	19.4	137	8.1	16	10.5	
EGP score: last profession									
Blue collar	563	38.8	53	35.8	457	32.8	37	30.6	
Lower white collar	206	14.2	14	9.5	350	25.1	41	33.9	
Upper white collar	436	30.0	58	39.2	212	15.2	17	14.0	
Other	247	17.0	23	15.5	376	27.0	26	21.5	
U&S score: last profession									
1 (lowest)	301	20.7	25	16.9	449	32.2	39	32.2	
2 3	369	25.4	32	21.6	215	15.4	19	15.7	
	400	27.5	38	25.7	444	31.8	39	32.2	
4	207	14.3	19	12.8	79	5.7	7	5.8	
5 (highest)	175	12.1	34	23.0	19	1.4	2	1.7	
6 housewife					189	13.5	15	12.4	

^aOnly for women. ^bFor parous only. ^cThe index is based on the physical activity at work from the age of 20 until 1986 and is therefore age dependent.

ence in distribution of the SES indicators between cases and subcohort.

The association between SES indicators and covariates was studied in the subcohort by means of comparing mean values of age, Quetelet index, alcohol intake and the prevalence of cholecystectomy, large bowel cancer in the family and high physical activity at work between SES categories (Table II). Mean values of parity and age at first birth were only studied for women. In general, higher mean age, higher mean Quetelet index, lower mean alcohol intake and a higher percentage high physical activity at work were associated with a lower SES. For women higher prevalence of cholecystectomy was also associated with a lower SES, while for men the prevalence of cholecystectomy was slightly higher among whitecollar workers and high social standing professions. Mean parity was higher in the lowest SES groups and age at first birth was somewhat higher among women with a higher SES. The prevalence of large bowel cancer in the family was slightly higher among people with a higher educational level or a white-collar occupation.

The results of the stratified analyses are presented in Table III. After adjustment for age in three 5 year categories, for men there was a non-significant positive association between level of education and colon cancer risk (RR highest/lowest level of education = 1.41; trend P = 0.13). Male upper white-collar workers had a higher rate ratio than blue-collar workers (RR = 1.42; 95% CI = 0.95-2.11), but lower white-collar workers had a lower colon cancer rate. Also, a significant positive association between U&S score and colon cancer risk was observed for men (RR high/low social stand-

Table II Association between possible confounders and SES indicators in the subco	Table I
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	Hi	ghest level							~
	education ^a				EGP			S	
Characteristic	Low	Medium	High	Blue	White	Other	Low	High	Housewife
Men									
Age (mean years)	61.9	61.3	61.1	61.3	61.1	61.8	61.4	61.2	
QI (mean kg m ^{-2})	25.4	24.9	24.6	25.2	24.7	24.8	25.3	24.6	
Alcohol intake (mean g day ⁻¹)	12.3	13.7	18.3	12.5	17.7	10.8	12.5	16.2	
Cholecystectomy (% yes)	4.4	4.5	5.0	4.1	5.0	4.0	3.9	5.3	
Large bowel cancer in family (% yes)	4.6	5.2	5.5	4.6	4.8	7.3	5.2	5.1	
Physical activity at work (% high)	34.6	23.4	2.6	40.0	4.7	21.7	38.9	5.8	
Women									
Age (mean years)	62.3	61.0	61.1	61.3	61.2	61.1	61.1	61.3	61.2
$OI (mean kg m^{-2})$	25.8	25.1	23.8	25.8	24.4	25.3	25.5	24.5	25.7
Alcohol intake (mean g day ⁻¹)	3.8	6.0	9.4	4.5	7.6	5.0	5.1	7.2	4.7
Parity (mean)	2.7	2.5	1.8	2.8	1.7	2.9	2.7	1.7	3.2
Age at first birth ^c (mean years)	26.3	27.0	27.0	26.5	27.8	26.7	26.6	27.8	26.6
Cholecystectomy (% yes)	15.4	13.0	10.8	13.9	10.9	15.2	13.3	11.3	16.4
Large bowel cancer in family (% yes)	4.5	5.5	7.6	4.6	5.3	4.5	5.1	4.6	4.8
Physical activity at work (% high)	34.8	19.3	12.3	31.8	17.1	16.7	28.6	15.4	

^aHighest level of education: low, primary school; medium, lower vocational or junior high school; high, senior high school, higher vocational or university. ^bLow social standing: U&S categories 1 and 2; high social standing: U&S categories 3, 4 and 5. ^cFor parous only.

Table III	Age-adjusted	Mantel-Haenszel	rate	ratios	and	multivariatea	rate	ratios	for	colon	cancer	according	to	three	different	SES
						indicators						-				

				indicators				
			Men				Women ^b	
SES indicator	No. of cases in cohort	Person years in subcohort	RR_{мн} (95% CI)	RR (95% CI) multivariate ^a	No. of cases in cohort	Person years in subcohort	RR_{MH} (95% CI)	RR (95% CI) multivariate ^a
Highest level of education								
Primary school	38	1455	1*	1*	54	1959	1*	1*
Lower vocational	33	1098	1.24 (0.76-2.04)	1.18 (0.68-2.03)	33	1240	1.04 (0.64 - 1.69)	1.49 (0.80-2.78)
Junior high school	35	1345		0.68(0.38 - 1.21)	42	1551		0.96 (0.54 - 1.72)
Senior high school Higher vocational/	19	397		1.58 (0.82-3.06)	8	280		1.22 (0.47-3.16)
university Test for trend	30	883	1.41 (0.84-2.35)	1.00 (0.54-1.84)	16	450	1.31 (0.71-2.39)	0.88 (0.39-1.99)
χ^2 (<i>P</i> -value)			2.33 (0.13)	0.03 (0.86)			0.61 (0.43)	0.15 (0.69)
EGP score: last profession								
Blue collar	53	1803	1*	1*	37	1475	1*	1*
Lower white collar	14	667	0.69 (0.37 - 1.28)	0.56 (0.27 - 1.13)	41	1139	1.46(0.91 - 2.33)	1.30 (0.76-2.22)
Upper white collar	58	1404	1.42 (0.95-2.11)	1.09 (0.65-1.83)	17	696		0.63 (0.30-1.29)
Other ^c Test for trend	23	798	0.95 (0.57–1.58)	0.71 (0.39–1.30)	26	1222	0.85 (0.51-1.43)	0.72 (0.34-1.50)
χ^2 (<i>P</i> -trend)			2.70 (0.10)	0.91 (0.34)			0.05 (0.82)	0.61 (0.43)
U&S score: last profession								
1 (lowest)	25	969	1*	1*	39	1456	1*	1*
2	32	1188	1.05 (0.61 - 1.81)	1.10 (0.60-2.03)	19	697	0.96 (0.54 - 1.70)	0.93 (0.50 - 1.75)
3	38	1282		1.26(0.66-2.41)	39	1449	· · · · · · · · · · · · · · · · · · ·	0.79 (0.46 - 1.35)
4	19	667	```	1.12 (0.52-2.39)	7	259		0.63 (0.24 - 1.66)
5 (highest)	34	564		2.60 (1.31-5.15)	2	62		0.82 (0.17 - 3.84)
6 housewife ^c Test for trend			. ,		15	610	0.93 (0.50-1.73)	
χ^2 (<i>P</i> -value)			7.05 (0.008)	7.83 (0.005)			0.00 (0.98)	1.19 (0.28)

*Reference category. *Multivariate analyses with adjustment for age, Quetelet index, cholecystectomy, alcohol intake, large bowel cancer in family and physical activity at work. ^bAdditional adjustment for parity and age at first birth. ^cExcluded for test for trend. ^dWithout the category housewives for reasons of multicollinearity with physical activity during work.

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ing = 2.42, 95% CI 1.39-4.20, trend P = 0.008). These positive associations between SES and colon cancer were not found in women.

Table III shows also the results of the multivariate analyses in which adjustment was made for age, Quetelet index, cholecystectomy, alcohol intake, large bowel cancer in the family and physical activity during work. For women additional adjustment was made for parity and age at first birth. After adjustment there was no clear association between level of education and colon cancer risk for men or for women; subjects with lower vocational school or senior high school had the highest adjusted colon cancer rate, but the colon cancer rate of people with higher vocational training or university was close to 1. The association between EGP score and colon cancer risk is also inconsistent. A significant positive association between U&S score and colon cancer rate remained after additional adjustment for men (trend P = 0.005), but the higher risk was only found in the group with the highest U&S score (RR highest/lowest = 2.60, 95% CI 1.31-5.15). This association was not seen among women.

We have also conducted multivariate analyses including energy intake and the intake of dietary fibre as additional covariables. This did not change the association between colon cancer and the SES indicators (not presented).

Discussion

We have found a significant positive association between social standing (U&S score) and colon cancer risk for men. This association persisted after adjustment for age, Quetelet index, cholecystectomy, alcohol intake, large bowel cancer in the family and physical activity during work, but was restricted to the highest category of social standing. The positive association between highest level of education and colon cancer risk in men became inconsistent after adjustment for the covariates mentioned above and the colon cancer rate of subjects with the highest level of education was similar to the colon cancer rate of subjects with the lowest level of education. According to the EGP score, male upper white-collar workers had, after adjustment, almost the same colon cancer rate as blue-collar workers. For women the association between EGP score and colon cancer was opposite to that for men, with the highest risk among the lower white-collar workers. But none of these associations was significant. There were no associations found between the other two SES indicators and colon cancer risk in women.

The non-significant positive association between level of education and colon cancer risk for men observed in our study is similar to results from cross-sectional (Williams and Horm, 1977; Faivre et al., 1989) and case-control (Papadimitriou et al., 1984; Ferraroni et al., 1989) studies on education and colon cancer. In a cohort study in Finland (Pukkala and Teppo, 1986) significant positive associations between level of education and colon cancer incidence were reported, with the highest risk for men with high school education, whereas in a cohort study in England a nonsignificant inverse association between level of education and colon cancer risk was reported for men (Leon, 1988). This is probably due to the categorisation of education in two categories, with only 12.6% of the men being in the highest category. The association between education and colon cancer risk is not clear for women. A correlation study (Baquet et al., 1991), a cross-sectional study (Faivre et al., 1989) and a case-control study (Bidoli et al., 1992) reported no association between education and colon cancer risk for women, while an inverse association was found in a crosssectional study (Williams and Horm, 1977), and in two cohort studies in Scandinavia (Pukkala and Teppo, 1986; Vågerö and Persson, 1986) significant positive associations were reported. We did not find an association between education and colon cancer, which is consistent with the finding that health differences between SES categories for women are

smaller in The Netherlands than in most other European countries and North America (Kunst *et al.*, 1993), probably because of relatively small differences in education within the female population.

Almost all studies that used occupation as SES indicator reported significant positive (age-adjusted) associations for men (Pukkala and Teppo, 1986; Vågerö and Persson, 1986; Leon, 1988; Bidoli et al., 1992), similar to our results. One study found only a positive association with left colon cancer and not with right colon cancer (Faivre et al., 1989). Owing to a limited number of cases our study could not differentiate between left and right colon cancer. Those studies that also reported a significant positive association for women used the occupation of the head of household as SES indicator (Pukkala and Teppo, 1986; Bidoli et al., 1992), or was restricted to economically active persons (Vågerö and Persson, 1986). We did not find an association between the occupation-based SES indicators for women. All women were classified according to their last occupation, although almost 50% of the women finished their formal employment 30 years ago, which is typical for The Netherlands (Hooghiemstra and Niphuis-Nell, 1993). This resulted in a substantial proportion of housewives among women in the cohort. The SES measures based on the last occupation therefore have only limited value for women in the NLCS.

In only one study was adjustment made for potential risk factors for colon cancer other than age and place of residence: a non-significant association between colon cancer and education or occupation was found after adjustment for age, sex, marital status, smoking, coffee and alcohol consumption (Ferraroni et al., 1989). In our study the positive association between highest level of education and colon cancer disappeared after adjustment for age, cholecystectomy, Quetelet index, alcohol consumption, large bowel cancer in the family and physical activity at work. Also, after adjustment, the higher risk of upper white collar workers became similar to the rate of blue-collar workers. The significant positive association between social standing (U&S) and colon cancer risk persisted after adjustment was made, but the significantly higher risk was only found in the highest U&S category. We found a slightly higher prevalence of cholecystectomy and a higher mean alcohol intake in this group, compared with the second highest U&S group (not presented), but since we adjusted for these potential confounders this cannot explain the difference in relative rates. Unfortunately none of the studies on SES and colon cancer used a prestige-based SES indicator, as a result of which we cannot compare our finding with other studies.

The cohort study has been performed in a large sample of the general population aged 55-69 years at baseline. The follow-up period of 3.3 years resulted in 157 male and 155 female colon cancer cases, indicating that the study had reasonable but not very large power, because in general about 400 cases are needed to detect relevant associations (Phillips and Pocock, 1989). Therefore, a longer follow-up period is warranted to study this association in a more definitive way. Another disadvantage of the still limited length of follow-up could be a high proportion of cases diagnosed in the first year of follow-up, with the possibility of change in exposure owing to symptoms of prediagnostic cancer. Fortunately, education and occupation are relatively fixed and would have preceded even occurrence of these cases. The follow-up of person-years was 100% complete, and the completeness of cancer follow-up was also very high, indicating that selection bias due to loss to follow-up is unlikely.

Although known risk factors for colon cancer were measured and controlled for in the multivariate analyses, residual confounding by physical activity could still have existed, since a relatively crude physical activity score was used to classify occupations, possibly resulting in misclassification. The intake of ethanol $(g day^{-1})$ divided into five categories was used to control for alcohol intake. Residual confounding due to alcohol consumption is unlikely because alcohol consumption has shown to be hardly related to colon cancer in this data set (Goldbohm *et al.*, 1994b). Only one study on SES and colon cancer adjusted for alcohol intake, and none of the studies paid attention to physical activity or other confounders.

Another fact that could have influenced the results is misclassification of exposure. SES is operationalised as highest level of education, EGP score (functional level) and U&S score (social standing), the last two both based on the last occupation. Highest level of education is a characteristic that is easily obtainable and recordable. It applies to every adult individual, and in individuals it is stable over time, thus avoiding the risk of reverse causation. This stability has also negative implications for the suitability of level of education as SES indicator, since it can mask important changes in individual circumstances after education is completed (Zurayk et al., 1987). Therefore highest level of education is probably a less relevant SES indicator for the older generation (Thijssen, 1986). The occupation-based SES indicators reflect the more recent situation, but occupational status as SES indicator leads to the problem of how to classify persons without formal occupation, such as the large majority of women with no formal employment. In our study, women are classified according to their last occupation and there is a separate category of housewives for women who have never had a formal occupation. Another possibility is to use the occupation of the husband or head of household when the person of interest has no formal employment. Unfortunately, we did not have that information.

Detection bias may be another concern in colon cancer studies. In The Netherlands, however, there is no mass screening of subjects without symptoms of colorectal cancer.

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A first colonoscopy is only performed in patients with gastrointestinal complaints or in family members of patients with hereditary colorectal cancer. Because there are no large differences in access to medical care between SES categories in The Netherlands, this is not likely to lead to a higher detection of colon cancer within the higher SES groups.

In conclusion, we found a positive age-adjusted association between colon cancer risk and three SES indicators for men. After additional adjustment for Quetelet index, cholecystectomy, alcohol intake, large bowel cancer in the family and physical activity during work, the association between colon cancer risk and social standing remained significant, although the higher risk was only found in the highest social standing category. We found no clear associations between the SES indicators and colon cancer incidence for women. More research on differences in colon cancer risk between men and women is warranted, to find out whether these differences are mainly due to differences in the meaning of SES for men and women or if these differences are related to differences in the distribution of risk factors.

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