

# The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands

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## ABSTRACT

**Background:** Subjects with a positive family history of colorectal cancer (CRC) have an increased risk of developing CRC themselves. This risk depends on the number of affected relatives and the age at diagnosis.

**Aim:** The aim of this study was to assess the prevalence of a positive family history of CRC, within a random cohort among the Dutch population.

**Methods:** A total of 5072 subjects aged between 45 and 70 years were invited to fill in an anonymous questionnaire about the occurrence of CRC in their first-degree relatives (FDR).

**Results:** The questionnaire was returned by 3973 subjects (78.3%). Thirty responders (0.8%) had CRC themselves. Of all unaffected responders, 441 (11.2%) subjects reported a positive family history of CRC. Ninety (2.3%) responders reported having an FDR with CRC diagnosed before the age of 50, or reported two or more FDRs with CRC.

**Conclusion:** The prevalence of a positive family history of CRC is substantial. Identification of this high-risk group by obtaining a thorough family history is the first step in targeting preventive measures.

## KEYWORDS

Familial colorectal cancer, general population, prevalence

## INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in well-developed countries. Most cases of CRC (around 80%) are probably caused by environmental factors. In up to 5% of all colorectal cancers, genetic factors play a dominant role.<sup>1,2</sup> The most common

hereditary syndromes are Lynch syndrome (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP).<sup>3-6</sup> Predisposed individuals from Lynch syndrome families have a life-time risk of developing CRC of 60 to 85%,<sup>7,8</sup> individuals from MAP families have a life-time risk of 50 to 60%<sup>9</sup> and polyposis patients almost inevitably develop CRC if they are left untreated.

In around 10 to 15% of all CRC cases, a positive family history of colorectal cancer is observed. It is probable that dietary and other environmental risk factors,<sup>10</sup> acting solely or in concert with genetic factors, influence aggregation of the disease.<sup>11</sup>

The risk associated with a family history of CRC depends on the number of affected relatives and the age at diagnosis.<sup>12-14</sup> Subjects with one FDR with CRC diagnosed at age >50 years have a relative risk (RR) of developing CRC of 2 to 3.<sup>15</sup> Subjects with two (or more) FDR with CRC diagnosed at any age, or with one FDR with CRC diagnosed before the age of 50 years have a relative risk of 4 to 6 for developing CRC.<sup>13,16-18</sup>

Surveillance is strongly recommended for subjects from families with hereditary syndromes. Most experts also advise colonoscopic surveillance for subjects with a moderately increased risk of developing CRC (RR  $\geq 4$ ). In most countries subjects with one FDR with CRC >50 years of age are not offered regular colonoscopy. In the USA, surveillance colonoscopy is recommended from the age of 40, or ten years younger than the earliest diagnosis in their family, if one (or more) family member has been diagnosed with CRC or adenomatous polyps before the age of 60.<sup>19,20</sup> The proportion of the Dutch population with an increased risk of developing CRC on the basis of a positive family history is unknown. We need to know the size of this high-

risk group when planning public health programmes aimed at reducing incidence and mortality from this disease, as those at higher risk can be subject to more intense strategies. The aim of this study was to assess the prevalence of the frequency of a positive family history of CRC, within a random cohort among the Dutch population.

## PATIENTS AND METHODS

The study was performed in a rural town, Coevorden, which is located in the east of the Netherlands. Approximately 16,500 subjects are registered with one of the nine general practitioners of this town. All subjects aged between 45 and 70 years ( $n = 5072$ ) (30.8%) were eligible for the study. In the first week of January 2005, these subjects were invited on behalf of their general practitioner to complete a short questionnaire and to return it within two weeks. The questionnaire included questions on current age, gender of the participant, the number of brothers and sisters; and on the occurrence of CRC (and age of diagnosis) in any of their FDR (father, mother, sibling, children). The questionnaire was anonymous, which means that we were not able to confirm the diagnosis of colorectal cancer.

In order to evaluate whether this sample was representative for the Dutch population, we compared the age distribution of our cohort with the general Dutch population (<http://statline.cbs.nl>).

For statistical analyses the Fisher's exact test was used. The study was approved by the ethics committee of the Leiden University Medical Centre.

## RESULTS

Completed questionnaires were received from 3973 (78.3%) of the 5072 subjects. *Table 1* shows the proportion of subjects aged 45 to 70 years for the study cohort and the general population. No difference was observed in the age distribution. Females and elderly people responded more often than males and younger subjects (*table 1*). Thirty responders (0.8%; 63% male) had a history of colorectal cancer themselves. Seven of them (23.3%) were diagnosed before the age of 50 years. Six of these 30 responders (20.0%) had one ( $n=3$ ) or two ( $n=3$ ) FDR with CRC.

Of all unaffected responders ( $n=3943$ ), 441 subjects (11.2%) reported having one ( $n=399$ ) or more ( $n=42$ ) FDR with CRC. Of the responders, 306 (7.8%) had a parent with CRC and three subjects (0.08%) a child. A total of 158 (4.2%) of 3757 unaffected responders with at least one sibling reported having a sibling with CRC. Of all unaffected responders, 90 subjects (2.3%) reported having two or more FDRs with CRC or one FDR with CRC diagnosed at age <50 years. Ten subjects (0.3%) had three or more FDRs with CRC. In *table 2*, the results are summarised.

**Table 1.** Age distribution in Dutch population and in Coevorden and number of receivers and responders of the questionnaire

Age	General population 2004		Receivers		Responders		
	Total	Total	Male	Female	Total	Male	Female
45-49 years	1,183,325	1185	612	573	822 (69.4)	399 (65.2)	423 (73.8)
50-54 years	1,113,623	1134	622	512	893 (78.7)	465 (74.8)	428 (83.6)
55-59 years	1,084,753	1013	492	521	811 (80.1)	378 (76.8)	433 (83.1)
60-64 years	795,586	866	421	445	719 (83.0)	346 (82.2)	373 (83.8)
65-70 years	663,208	874	440	434	728 (83.3)	358 (81.4)	370 (85.3)
Total (% of population)	4,840,495 (29.8%)	5072 (30.8%)	2587	2485	3973 (78.3)	1946 (75.2)	2027 (81.6)

**Table 2.** Number of unaffected responders and their family history

Family history	Number of responders* (%)
Total	3943
No colorectal cancer in direct family	3502 (88.8)
≥1 first-degree relative with colorectal cancer	441 (11.2)
1 first-degree relative, diagnosed at age <50	48 (1.2)
2 first-degree relative, any age	32 (0.8)
• 2 first-degree relative, 1 diagnosed at age <50	6 (0.2)
≥3 first-degree relative, any age	10 (0.3)
• ≥3 first-degree relative, 1 diagnosed at age <50	3 (0.08)

\* Responders without a history of colorectal cancer.

The proportion of responders with at least one affected FDR increased with the age of the (unaffected) responder; the proportion was 9.1% in the responders aged between 45 and 49 years, 10% in the age group 50 to 54 years, 11.6% in the age group 55 to 59 years, 12.5% in the age group 60 to 64 years and 13.1% in the age group 65 to 70 years. The difference between the youngest and oldest age group was statistically significant ( $p=0.02$ , two-sided Fisher's exact test).

For 3850 out of the 3973 responders, we received information about the number of siblings. The responders had a total of 15,721 siblings. The average number of siblings in our cohort (including the responder) was 5.1 per family, (range 1 to 18; median 4). The proportion of families with at least one affected sib significantly increased with the size of the family ( $p<0.0001$ ,  $\chi^2$  test): in families with 1 to 3 siblings, this proportion was 3.1% (43/1385), in families with 4 to 6 siblings it was 4.6% (66/1432), in families with 7 to 9 siblings it was 6.4% (44/691), in families with 10 to 12 siblings it was 9.5% (24/253), and in families with 13 to 15 siblings it was 11.8% (9/76). Only 14 families had 16 to 18 siblings, and in one family a sib was affected with CRC (7.7%).

## DISCUSSION

This study is the first manuscript on the prevalence of a positive family history of CRC among a large, population-based, Dutch cohort of subjects aged between age 45 and 70 years. Of all subjects in this age group, 11.2% had at least one FDR with CRC, 2.3% of the responders had two or more FDRs with CRC or had one FDR with CRC diagnosed at age <50 years, and 0.3% of the subjects had three or more FDRs with CRC. A positive family history was associated with the size of the family and age of the index person.

Most studies on family history of CRC were performed in cohorts of patients with CRC.<sup>12-14,18,21,22</sup> These studies reported a proportion of 10 to 15% of the index cases having an FDR with CRC. In the present series, this proportion was higher (20%) but the number of CRC cases ( $n=30$ ) in our series was relatively small.

Information on the prevalence of a positive family history of subjects not affected with CRC may be derived from case-control studies.<sup>13,16,18,22</sup> The reported family history for colorectal cancer in the control groups varied in these studies from 4 to 10%. However, these figures are probably not representative for the population prevalence, because cohorts of controls will be elderly people when matched by age with CRC patients in case-control studies. The potential bias of the elderly is minimised in the study by Fuchs *et al.*<sup>16</sup> They studied two groups of health care professionals, aged 30 to 75 ( $n=119,116$ ). The reported family history of CRC among their FDRs was similar (10%) to our study.

Several factors could influence the present findings and might result in an over- or underestimation of the true prevalence of a positive family history. First, our study is based on the reported family histories and not on pathology reports. Indeed some studies reported that the accuracy of self-reporting for CRC is not very good.<sup>23-25</sup> Other studies on the reliability of a family history showed that patient-reported family cancer histories of FDR are accurate and valuable for colon cancer risk assessments.<sup>26,27</sup> Second, despite the high response rate (78.3%) in this study, it can not be excluded that subjects with a positive family history for CRC responded more often than subjects with unaffected FDRs. Moreover, the responders were more often female and of an older age than all subjects who received a questionnaire. This may also influence the results. Third, the prevalence of a positive family history depends on the size of the family, and the age of the responder. With respect to age, the proportion of subjects in age group 45 to 70 years in Coevorden is similar to that of the general population (*table 1*). However, within this age group there are some differences between the general population and the studied population (*table 1*). Unfortunately, information on differences in family size between Dutch regions is not available. At the national level, the mean number of siblings in each family is not available either. Although such information is not available, the impression from this study is that we are dealing with relatively large families with many siblings per family. If this is indeed the case, this might have led to overestimation of the calculated prevalence of a positive family history. Environmental factors can also effect the frequency of (familial) colorectal cancer. However, according to data from the National Cancer Registry, there are no significant differences in CRC incidence between regions within the Netherlands. Although it seems rather difficult to be sure how representative the risk of colon cancer in the city of Coevorden is for the Netherlands as a whole, we think that our results are representative for the general Dutch population.<sup>28</sup>

Our study demonstrated that the proportion of subjects in the general population with an increased risk of developing CRC based on their reported family history is substantial. Based on the findings, we estimate that more than 500,000 subjects in the Netherlands in the age group 45 to 70 years have an at least two to three times increased risk of developing CRC. Approximately 100,000 of these subjects have an increased relative risk of four or more. If all subjects with a positive family history are identified and encouraged to participate in surveillance protocols, more than 10 to 15% of all colorectal cancers (900 to 1400 cases every year in the Netherlands) might be prevented. Colonoscopy is currently the appropriate surveillance method for this high-risk group. Studies are needed to elucidate the best surveillance interval for this high-risk group.

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