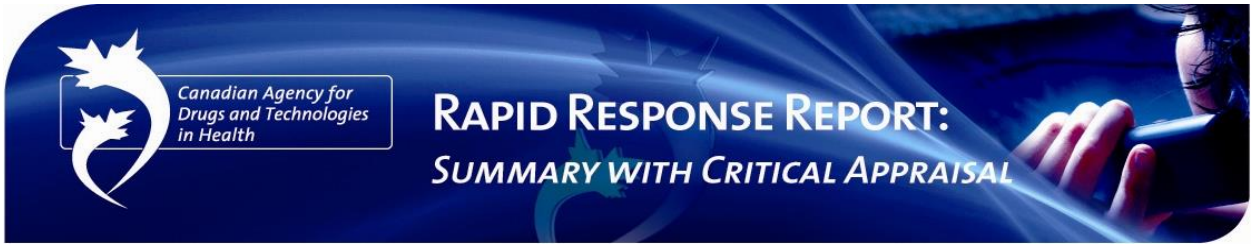

TITLE: **Cancer Surveillance for Family Members of Patients with Colorectal Cancer with or without Mismatch Repair Deficiency: A Review of the Clinical Evidence**

DATE: 06 July 2015

CONTEXT AND POLICY ISSUES

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in Canada.[1] It is estimated that about 25,100 Canadians will be diagnosed with CRC in 2015 and 9,300 will die from it.[1] Based on family history, CRC can be classified as sporadic (75%) and hereditary (25%).[2] Patients with sporadic disease have no apparent evidence of inheritance.[2] Of the hereditary CRC syndromes, hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome accounts for about 2 to 5% of CRC cases overall.[3]

The two terms HNPCC and Lynch syndrome are used interchangeably to describe the hereditary pattern of CRC caused by mutations in mismatch repair (MMR) genes.[4] Individuals with Lynch syndrome have a high risk of developing CRC (lifetime risk 30 to 70%), endometrial cancer (life time risk 30 to 60%), and other cancers at a younger age compared to the general population.[5] The four common DNA repair genes known to be associated with Lynch syndrome are *MLH1*, *MSH2*, *MSH6* and *PMS2*.[6] Mutation in the MMR genes leads to the loss of MMR protein expression and DNA microsatellite instability (MSI).[7]

Microsatellites are short repeated base sequences found predominantly in the non-coding regions of DNA that are vulnerable to replication errors.[6] When MMR genes are mutated, the ability to correct replication errors is lost, resulting in the production of microsatellite copies of variable lengths (microsatellite instability) in the daughter cells that are different from the mother cells.[8] MSI testing uses a PCR-based assay in tumor-derived DNA to detect the instability at selected microsatellite loci.[7] Alternatively, loss of MMR protein expression due to MMR gene mutations can be detected using an immunohistochemical technique (IHC).[7]

Tumors that have MSI or loss of MMR protein are referred to as MMR-deficient (also referred to as dMMR).[9] MMR-proficient tumors include those with stable microsatellites, low-frequency MSI, or intact MMR proteins by IHC.[9] A potential clinical diagnosis of HNPCC/Lynch syndrome is made based on a detailed family history of cancer according to the Amsterdam criteria I and II, but a definitive diagnosis of HNPCC/Lynch Syndrome is made through the identification of a germline MMR mutation.[8] However, not all patients who meet the Amsterdam criteria have a germline mutation in one of the MMR genes; some of these have an occult MMR gene mutation associated with dMMR tumors, whereas others have MMR-proficient tumors due to another

CRC predisposition syndrome or simply a chance clustering of common cancers.[9] In this review, HNPCC, Lynch syndrome and mutation positive are used interchangeably, and it is assumed that Lynch Syndrome is associated with a germline MMR mutation. Members of Lynch syndrome families could be either mutation positive (mutation carriers) or mutation negative (non-mutation carriers). Close surveillance of members of Lynch syndrome families has been shown to decrease the risk of cancer-related mortality.[10] In 2000, the results of colonoscopic surveillance (screening and polypectomies) at 3-year intervals of 22 families with HNPCC showed that members who entered the surveillance program had significant reduction in the rates of CRC and death compared to those who declined screening.[11]

The aim of this report is to review the clinical effectiveness of cancer surveillance for family members of patients with colorectal cancer with or without mismatch repair deficiency.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of surveillance of family members of colorectal cancer patients with Lynch Syndrome or mismatch repair deficient tumours?
2. What is the clinical effectiveness of surveillance of family members of mismatch repair proficient colorectal cancer patients?
3. What is the comparative clinical effectiveness of surveillance of family members of colorectal cancer patients with Lynch Syndrome or mismatch repair deficient tumours compared with those who are proficient?

KEY FINDINGS

Surveillance was associated with decreased risk of colorectal and extra-colonic cancers, early cancer detection, and better survival in members of HNPCC families, regardless of mutation status. No evidence could be found regarding surveillance of family members of mismatch repair proficient colorectal cancer patients.

During surveillance, higher rates of colorectal and other cancers were detected in mutation carriers (mutation positive) or members of Lynch syndrome families compared with non-mutation carriers (mutation negative) or members of non-Lynch syndrome families, respectively. There was no difference in the risk of mortality between mutation positive and mutation negative individuals, which suggests a potential benefit of screening for Lynch Syndrome for family members.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and June 5, 2015.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1, 3: Family members of mismatch repair deficient colorectal cancer patients Q2: Family members of mismatch repair proficient colorectal cancer patients
Intervention	Surveillance and monitoring (e.g. colorectal cancer screening, cancer screening)
Comparator	Q1, 2: No surveillance Q3: Surveillance of family members of mismatch repair proficient colorectal cancer patients
Outcomes	Clinical effectiveness (e.g. improved morbidity and mortality)
Study Designs	Health technology assessments (HTA), systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2005, duplicate publications of the same study, or included in a selected health technology assessment or systematic review.

Critical Appraisal of Individual Studies

The quality of the HTA was assessed using AMSTAR.[12] Non-randomized study quality was evaluated using the Downs and Black instrument.[13]

For the critical appraisal of studies, a numeric score was not calculated. Instead, the strength and limitations of the studies were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 491 citations. Upon screening titles and abstracts, 20 potential relevant articles were retrieved for full-text review. Three additional relevant reports were retrieved from other sources. Of the 23 potentially relevant articles, nine reports were included in this review including one HTA, eight observational studies (seven prospective and one retrospective surveillance studies). The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

The characteristics of the included studies[14-22] are summarized in Appendix 2.

The heath technology assessment (HTA)[14] prepared for the Agency for Healthcare Research and Quality (AHRQ) had a broad scope for HNPCC and included 104 studies addressing 40

issues related to clinical validity for predicting the presence of HNPCC in patients with colorectal cancer, analytical validity in evaluating patients for HNPCC, and benefits and harms related to screening and testing patients with CRC and their family members for HNPCC. For outcomes relating to subsequent follow-up of members of HNPCC families, the HTA included eight studies including six retrospective studies, one prospective studies and one RCT. Of those studies, only four, with low quality (Level C), had outcome results comparing between family members who received surveillance versus those who did not.

Of eight included observational studies, seven[15-20,22] were prospective and one[21] was retrospective. All studies had a defined surveillance period, which varied from 4 years[18] to 44 years.[21] Survival or mortality was reported in three studies,[17,20,21] while risk of cancer (either CRC or extra-colonic cancers) was reported in all studies. Three studies[16,17,21] compared the risk of CRC or mortality in Lynch syndrome family members who underwent surveillance and in those who did not. Six studies[15,16,18-20,22] compared the risk of cancer or mortality in mutation carriers versus non-mutation carriers. Individuals of Lynch syndrome families could be mutation carriers (mutation positive) or non-mutation carriers (mutation negative), while those of non-Lynch syndrome families were non-mutation carriers including those who fulfilled Amsterdam I or II criteria.

The Danish HNPCC-surveillance study included 2,959 at-risk women was published in 2014.[15] At-risk women were classified into three groups (676 women from Lynch syndrome families, 892 women from Amsterdam (AMS) I or II criteria positive families and 1,391 women from AMS-like families). Women who had undergone hysterectomy were excluded. All women were informed about HNPCC-related cancer risks and the recommended surveillance program. The gynecologic surveillance consisted of biennial gynecological examination, transvaginal ultrasound, and endometrial sampling of women from the age of 25 years. Data were collected from January 1, 1991 to September 15, 2011 (or until hysterectomy or death). Mean time of follow-up was 6.5 years (range: 0.1 to 21.7 years) or 19,334 women years. The main outcome was incidence of endometrial cancer.

The surveillance study in Chinese Lynch syndrome families (*MLH1* and *MSH2* mutations) registered in the General Hospital of Beijing Military Region was published in 2013.[16] A total of 263 members (at age 20 years and over) of 42 Lynch syndrome families with completed genetic analysis received genetic counselling and underwent colonoscopic surveillance. Colonoscopy was repeated every 1 to 2 years for mutation carriers (n=144) and once in 5 years for non-mutation carriers (n=119). Sixty-five individuals received additional tests including gastroscopy, abdomen ultrasound, computed tomography or other imaging examinations to assess Lynch syndrome-related extra-colonic tumors. Surveillance was carried out from May 2001 to October 2008. Colonoscopy surveillance was performed in 180 of 263 (68%), while 83 of 263 (32%) refused surveillance. The outcomes of interest were risk of CRC in mutation carriers and in non-mutation carriers, and the incidence of cancer detected (early and advanced) with or without colonoscopy surveillance.

The Canadian study was published in 2012 with the surveillance results on 18 Lynch syndrome families with *MSH2* mutation.[17] Family members at 50% risk of inheriting a mutation were invited to enter genetic screening. Of the 322 Lynch syndrome detected carriers, 152 (47%) entered CRC surveillance programme and 170 (53%) did not. Colonoscopy was repeated every 1 to 2 years starting at age 20 to 25 years. Median follow-up from entry to death or last follow-up was 9 years in males and 11 years in females. Eleven participants were excluded because they had only one colonoscopy. The outcomes of interest were risk of CRC and survival in individuals with and without surveillance.

The study from the German Consortium for HNPCC published surveillance results in 2010.[18] HNPCC family was defined as: 1) a mutation in the MMR genes (*MLH1, MSH2* or *MSH6*) was detected (MUT group), 2) no such mutation was found but at least one patient in the family showed a deficient MMR phenotype (MSI group), or 3) no patient with a MSI-H tumor was detected but the Amsterdam criteria was met (MSS group). A total of 1,126 individuals from 835 HNPCC families entered the colonoscopic surveillance and comprised patients with and without history of CRC (CRC^{pos} and CRC^{neg}) before inclusion in the study. Colonoscopy was performed annually, regardless of mutation status, starting at age 25 years. The accumulated observation time was 4,198 person-years. The outcome was risk of CRC in the MUT, MSI and MSS groups within the CRC^{pos} or CRC^{neg} groups.

The Netherlands national registry for families with hereditary CRC published surveillance results in 2010.[19] Surveillance was carried out from January 1, 1995 to January 1, 2009 in 745 mutation carriers of 205 Lynch syndrome families and 344 relatives of 46 non-Lynch syndrome families. Mean follow-up was 7 years (range: 0 to 14.2 years). Lynch syndrome families were those having known pathogenic (*MLH1, MSH2* or *MSH6*) mutations, while the non-Lynch syndrome families did not have mutations but met the Amsterdam criteria. Colonoscopy was repeated every 1 to 2 years, regardless of mutation status, starting at age 20 to 25 years. The outcome was risk of CRC in members of Lynch syndrome families (carriers) and those in the non-Lynch syndrome families.

The study from a centralized Finnish registry published the surveillance results of members of 57 Lynch syndrome families in 2009.[20] A total of 609 family members including 242 individuals who were mutation positive (carriers) and 367 individuals who were mutation negative. Follow-up time was at least 10 years (or to death) with a total of 2,536 and 4,151 person-years for carriers and mutation-negative participants, respectively. Colonoscopy was performed at a maximum of 3-year intervals for mutation-positive participants. For women, endometrial biopsy and transvaginal ultrasound were repeated every 2 to 3 years starting at age of 35 years. The mutation-negative family members did not have surveillance and served as the reference group. The outcomes were cancer risk and mortality in mutation carriers and mutation negative participants.

The Netherlands HNPCC surveillance study published the results of members of 140 Lynch syndrome families in 2006.[21] A cohort of 2,788 individuals including mutation carriers (n=882), putative carriers (n=310), and first-degree relatives of unknown carrier status (n=1,596) were followed up from January 1, 1960 to April 1, 2004 with a total of 92,196 person-years. Putative carriers were individuals with CRC or endometrial cancer (EC) detected before age 60 years and were not tested. Of all participants, 897 had surveillance colonoscopies, 1,073 did not have surveillance and 818 had unknown surveillance. It was unclear whether mutations carriers, putative carriers, and unknown carriers were balanced across surveillance groups. Colonoscopy was performed every 1 to 2 years starting at age 20 to 25 years. For women, transvaginal ultrasound was given every year starting at age of 30 to 35 years. The outcome was mortality in the surveillance and non-surveillance groups.

The colonoscopic surveillance study in the UK and the Netherlands published the results of 125 family members from 97 CRC patients.[22] Of the 288 participants, 91 were relatives of 29 Lynch syndrome families and 197 were relatives of 68 non-Lynch syndrome families. The surveillance period was from March 1, 1987 to December 31, 2003. Colonoscopy was repeated at least every 2 years starting at age 45 to 50 years. The outcome was risk of CRC in relatives of Lynch syndrome and non-lynch syndrome families.

Summary of Critical Appraisal

The strengths and limitations of the HTA[14] and the observational studies[15-22] are summarized in Appendix 3.

The methodological quality of the HTA[14] was very good, as 10 of the 11 items of the AMSTAR checklist were met. These include a priori design, duplicate study selection and data extraction, comprehensive literature search, not limiting inclusion by status of publication, providing list of included and excluded studies, providing characteristics of included studies, including quality assessment of included studies, conducting appropriate meta-analysis, and declaration conflicts of interest. The likelihood of publication was not assessed.

The quality of the observational studies (prospective, surveillance type),[15,16,19-22] was limited with respect to reporting, internal validity and power. For reporting, the characteristics of patients in the study were not described in six[15-22] out of eight studies, the characteristics of patients lost to follow-up and adverse events were not reported in all included studies. For internal validity, potential bias may arise in all included studies from the fact that outcome assessors were not blinded and follow-up was not the same for all participants. Also, confounding may occur since patients in different intervention groups were not recruited over the same period of time and patients were not randomized to intervention groups. None of the included studies reported power calculation for the primary outcomes and may not have had sufficient power to detect a clinically meaningful effect of the intervention.

Summary of Findings

The main findings and authors' conclusions of the included studies[14-22] are presented in Appendix 4.

A. Surveillance versus non-surveillance

One HTA[14] and three observational studies[16,17,21] had results comparing surveillance versus non-surveillance of members of HNPCC (Lynch syndrome) families.

The AHRQ HTA found that asymptomatic HNPCC family members, regardless of mutation status, who received colonoscopy surveillance, had a lower risk or developing CRC and extra-colonic cancers, lower mortality rates and increased survival compared to those who were not involved in screening.

The results from the surveillance study of 263 members in 42 Chinese Lynch syndrome families published in 2013 showed that surveillance had more early stage cancer detected (70.0% vs 36.5%, $P<0.01$) and fewer advanced cancers detected (30.0% vs 63.5%, $P<0.01$) compared to without surveillance.[16]

The surveillance results of 322 mutation carriers in 18 Lynch syndrome families in Canada published in 2012 showed that surveillance statistically significant reduced the risk of CRC compared to without surveillance (relative risk [RR] 0.29; 95% confidence interval [CI] 0.16 to 0.53).[17] Median survival in males and females who went through surveillance were 66 years and 80 years, respectively, compared to those did not go enter surveillance (52 years and 63 years, respectively). In males, the RR was 0.38; 95% CI 0.13 to 1.0; in females, the RR was 0.19; 95% CI 0.09 to 0.44.

The results of the Netherlands HNPCC surveillance study in 2,788 mutation carriers of 140 Lynch syndrome families published in 2006 showed that surveillance decreased the standardized mortality ratio by 73% compared to non-surveillance (6.4 vs 23.8, $P<0.001$).[21]

Taken together, surveillance of members of HNPCC families, regardless of their mutation status, was associated with a decreased risk of CRC and better survival.

B. Surveillance of mutation carriers versus non-mutation carriers within Lynch syndrome families, or members of Lynch syndrome versus members of non-Lynch syndrome families

Six studies[15,16,18-20,22] had results comparing mutation carriers versus non-mutation carriers, or members in Lynch syndrome families versus those in non-Lynch syndrome families.

The results of the Danish HNPCC-surveillance study published in 2014 showed that women in families with confirmed MMR mutations (Lynch syndrome) had a higher incidence rate of endometrial cancer (0.63 cases per 100 women years; *P*<0.0001) compared to those in families which met Amsterdam I or II criteria (AMS) (0.06 cases per 100 women years) or those in AMS-like families (0.05 cases per 100 women years).[15]

The results from the surveillance study of 263 members in 42 Chinese Lynch syndrome families published in 2013 showed that the incidence rate of CRC was 51% in mutation carriers compared to 0% in non-carriers (*P*<0.01) observed in 7 years follow-up.[16] A similar observation was made for other types of cancers (carriers: 8.3% vs non-carriers: 0%; *P*<0.01).

The surveillance study from the German Consortium for HNPCC included patients with (CRC^{pos}) and without (CRC^{neg}) a history of CRC.[18] The results published in 2010 showed that Lynch syndrome family members with MMR gene mutation (MUT) or without an MMR mutation but with microsatellite instability (MSI) had significantly higher CRC risk compared to those did not have mutations or MSI but met the Amsterdam criteria (MSS). In the CRC^{neg} group, the cumulative CRC risk at age 60 years for MUT or MSI was 23% (95% CI 14.8 to 31.2) compared to 1.8% (95% CI 0 to 5.1) for MSS. A similar observation was made in the CRC^{pos} group, with a CRC risk at age 20 years (MUT or MSI = 23.7%; 95% CI 14.5 to 32.9).

The surveillance results of the Netherlands national registry published in 2010 showed that the incidence rate of CRC was statistically significant higher in mutation carriers of Lynch syndrome families compared to relatives of non-Lynch syndrome families (4.4% vs 1.7%, *P*<0.05).[19] Similarly, the incidence rate of extra-colonic cancers was also higher in mutation carriers (24.4% vs 8.7%, *P*<0.001).

The results from the Finnish surveillance study of 57 Lynch syndrome families published in 2009 showed that the risk of cancer including CRC and others was statistically significant higher in mutation positive compared to mutation negative individuals (27% vs 5%; RR 5.80; 95% CI 3.43 to 9.50; *P*<0.00001).[20] However, the risk of overall mortality (6% vs 5%; RR 1.26; 95% CI 0.65 to 2.46; *P*=0.49) and the risk of cancer-related deaths (4% vs 2%; RR 2.28; 95% CI 0.82 to 6.31; *P*=0.49) were not statistically significant different in both groups. Of note, the mutation-negative family members did not have surveillance.

The results of the colonoscopic surveillance study in the UK and the Netherlands published in 2006 showed that the incidence rate of CRC was statistically significantly higher in relatives of Lynch syndrome families compared to those of non-Lynch syndrome families (4.4% vs 0.0%, *P*=0.010).[22] However, the risk of adenomas was similar in both groups (7.7% vs 7.6%; RR 1.15; 95% CI 0.6 to 2.3).

Taken together, mutation carriers (mutation positive) had higher risk of CRC and other cancers compared to non-mutation carriers (mutation negative). Similarly, members of Lynch syndrome families had higher incidence rate of CRC and extra-colonic cancers compared to those of non-Lynch syndrome families. However, the risk of mortality was similar between mutation positive and mutation negative individuals, based on one study.

Limitations

The studies included in the AHRQ HTA were of limited quality as they were of retrospective design and were published at or before 2006, during the period of which surveillance intervals and methods might be different than those currently recommended. The included studies might have selection bias and volunteer bias since the participants were not randomly assigned between groups and the baseline characteristics of the groups were not reported. Participants who agreed to undergo screening may have been in better heath than those who were not screened, and members with positive mutation or those from Lynch syndrome families were more likely to participate in surveillance and lived a healthier life style compared to those of negative mutation or members of non-Lynch syndrome families (performance bias). The numbers of individuals who were lost to follow-up or who did not enter surveillance were not reported leading to potential systematic differences in withdrawals between groups (attrition bias). Many studies had short observation times which were unable to correctly evaluate difference in the risk of mortality and survival between groups. As genetic analysis methods were not reported and might be different among studies, misclassification between Lynch and non-Lynch syndrome might occur in some studies, leading to incorrect estimation of the mutation effect. As the outcome assessors were unblinded, colonoscopic and gynecologic examinations might be performed more thoroughly in members of Lynch syndrome families or individuals with mutation positive than members of non-Lynch syndrome families or mutation negative individuals, leading to differences in cancer detection, but no difference in the risk of mortality (performance bias).

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence for clinical effectiveness of surveillance of members of HNPCC families (MMR deficient) or non-Lynch syndrome families (MMR proficient) was supported by the results of one HTA, seven prospective studies and one retrospective study. The quality of studies included in the HTA and in this review was limited. Compared with non-surveillance, colonoscopic and/or gynecologic surveillance was associated with decreased risk of CRC, early cancer detection, and better survival in members of HNPCC (MMR proficient or Lynch syndrome) families, regardless of mutation status. No evidence could be found for the clinical effectiveness of surveillance of family members of MMR proficient CRC patients (non-Lynch syndrome families). During surveillance, mutation carriers (mutation positive) and members of Lynch syndrome families had higher risk of developing CRC and other cancers compared with non-mutation carriers (mutation negative) and members of non-Lynch syndrome families. However, there was no difference in the risk of mortality between mutation positive and mutation negative individuals. This suggests a potential benefit to Lynch Syndrome screening for family members as the increased cancer risk did not result in a significant increase in overall or cancer-related mortality with a median follow-up of 11 years. However, it is possible that the follow-up time or study power were inadequate to detect infrequent or long-term events. Since the incidence rate of CRC remained high in mutation carriers despite surveillance, large-scale controlled trials using accurate surveillance methods are needed to identify optimal surveillance intervals.

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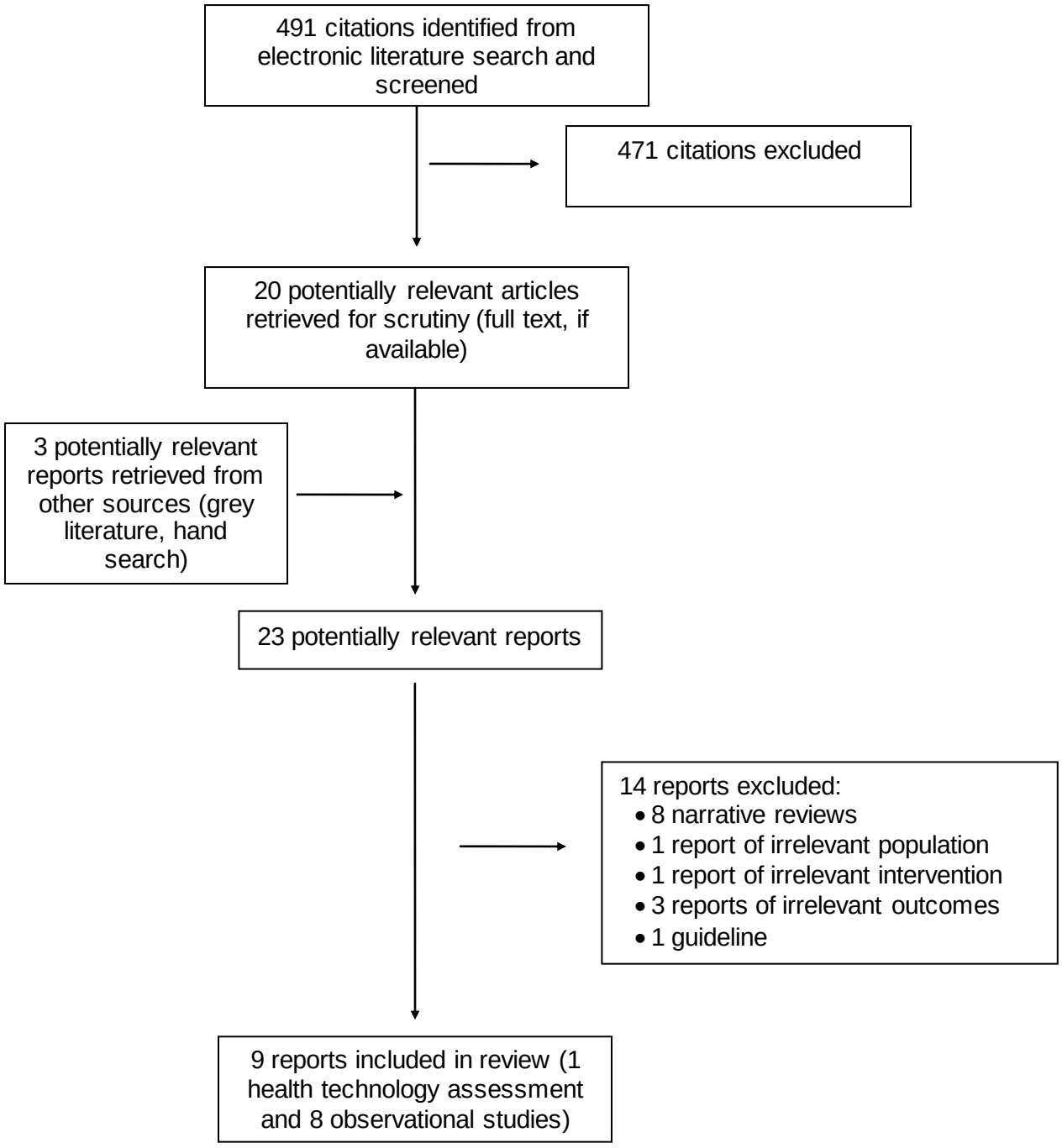
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient characteristics, sample Size (n)	Interventions	Clinical Outcomes
Health Technology assessment				
Bonis et al., 2007[14] USA	6 retrospective studies (0.1 to 82 years), 1 prospective study (6 months to 8 years) and 1 RCT (12 weeks)	HNPCC family members (mutation negative and mutation negative)	Colonoscopy and/or sigmoidoscopy surveillance versus non-surveillance	• CRC and EC risk • Mortality
Observational studies				
Ketabi et al., 2014[15] Denmark	Prospective study of the Danish HNPCC Registry Observation period: 1991 – 2011 Observation time: 19,334 women years Mean time of surveillance: 6.5 years (range: 0.1 to 21.7 years)	2,959 at-risk women from Lynch syndrome (n=676), Amsterdam I or II criteria (AMS) positive (n=892) and AMS-like (n=1,391) families	Gynecologic surveillance (January 1, 1991 to September 15, 2011) • Biennial gynecological examination • TVUS • Endometrial sampling Lynch vs AMS vs AMS-like	• Incidence of EC
Fu et al., 2013[16] China	Prospective study of the registry in the General Hospital of Beijing Military Region Observation period: 2001 – 2008	Family members (N=263) of 42 Lynch syndrome patients with completed genetic analysis Age: >20 years old Mutation carriers (n=144) Non-mutation carriers (n=119)	Surveillance (May 2001 to October 2008) • Colonoscopy repeated once in 1 to 2 years for mutation carriers and once in 5 years for non-mutation carriers • Gastroscopy, abdomen ultrasonic examination, CT or other imaging examinations (n=65) to assess Lynch syndrome-related extra-colonic tumors • Colonoscopy surveillance was performed in 180 of 263 (68%), while 83 of 263 (32%) refused surveillance	• Risk of CRC in mutation carriers and non-mutation carriers • Incidence of cancer detected with or without colonoscopy surveillance

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient characteristics, sample Size (n)	Interventions	Clinical Outcomes
			Mutation carriers vs non-mutation carriers With vs without surveillance	
Stuckless et al., 2012[17] Canada	Prospective study Median follow-up: 9 years in males and 11 years in females (or to death)	322 Lynch syndrome carriers: 152 (47%) entered CRC screening program and 170 (53%) did not	Surveillance (median follow-up: 9 years in males and 11 years in females) Colonoscopy (every 1 to 2 years starting at age 20 to 25 years) With vs without surveillance	• Risk of CRC • Survival
Engel et al., 2010[18] Germany	Prospective study from the German Consortium for HNPCC Observation time: 4,198 person-years (~3.7 years)	1,126 family members (with or without history of CRC) of HNPCC (Lynch syndrome) patients: • MMR gene mutation (MUT) • No MMR mutation but with MSI (MSI) • Fulfill AMS criteria without MSI (MSS)	Surveillance (observation time: 4,198 person-years) Annual colonoscopy from age 25 years or 5 years before the earliest disease manifestation within a given family MUT vs MSI vs MSS	• Risk of CRC
Vasen et al., 2010[19] The Netherlands	Prospective study from a national registry for families with hereditary CRC in the Netherlands Observation period: January 1, 1995 to January 1, 2009	745 mutation carriers of 205 Lynch syndrome families and 344 relatives of 46 non-Lynch syndrome families	Surveillance (observation period: January 1, 1995 to January 1, 2009) Colonoscopy (every 1 to 2 years starting at age 20 to 25 years) Lynch syndrome vs non-Lynch syndrome	• Risk of CRC
Jarvinen et al., 2009[20] Finland	Prospective study from a centralized Finnish registry Observation period: 11.5 years (or to death)	609 family members of 57 Lynch syndrome patients: • 242 mutation-positive (carriers) • 367 mutation-negative	Surveillance (11.5 years or to death) Colonoscopy (max 3 years intervals) Gynecologic examination (transvaginal ultrasonography) for	• Cancer risk • Mortality

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient characteristics, sample Size (n)	Interventions	Clinical Outcomes
			women (every 2 to 3 years starting at age of 35 years) Mutation-positive vs mutation-negative	
De Jong et al., 2006[21] The Netherlands	Retrospective study from the Dutch HNPCC Registry Observation period: 1960 – 2004 Observation time: 92,196 person-years	2788 members of 140 Lynch syndrome families (including mutation carriers (n=882), putative carriers (n=310), and first-degree relatives of unknown carrier status (n=1,596): • 897 had surveillance colonoscopies • 1073 did not have surveillance colonoscopies • 818 unknown surveillance	Surveillance (Observation period: January 1, 1960 to April 1, 2004) Colonoscopy (every 1 to 2 years starting at age 20 to 25 years) Gynecologic examination (transvaginal ultrasonography) for women (every year starting at age of 30 to 35 years) With vs without surveillance	• Mortality
Dove-Edwin et al., 2006[22] UK and The Netherlands	Prospective study from colonoscopic surveillance in the UK and the Netherlands Observation period: 1987 – 2003	288 family members from 97 CRC patients (Lynch syndrome and non-Lynch syndrome) • 91 relatives of 29 Lynch syndrome families • 197 relatives of 68 non-Lynch syndrome families	Surveillance (Observation period: March 1, 1987 – December 31, 2003) Colonoscopy (at least 2 years starting at age 45 to 50 years) Lynch syndrome vs non-Lynch syndrome	• Risk of CRC

AMS = Amsterdam I or II criteria; CRC = colorectal cancer; EC = endometrial cancer; HNPCC = hereditary non-polyposis colorectal cancer; MMR = mismatch repair; MSI = microsatellite instability; TVUS = transvaginal ultrasound; vs = versus

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Health Technology Assessment		
Bonis et al., 2007[14] USA	The methodological quality of this systematic review was very good as 10 out of 11 questions of the AMSTAR checklist scored "Yes"	The likelihood of publication bias was not assessed
AMSTAR check list 1. Was an "a priori" design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (i.e., grey literature) used as an inclusion criteria? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest stated?		
Observational studies		
Ketabi et al., 2014[15] Denmark	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Fu et al., 2013[16] China	*Reporting* • The objective was clearly described • The main outcome measures were clearly described	*Reporting* • The baseline characteristics of the patients included in the study were not described

First Author, Publication Year, Country	Strengths	Limitations
	Internal validity – confounding • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	• The characteristics of patients lost to follow-up were not described • Adverse events were not reported • Actual probability values were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Stuckless et al., 2012[17] Canada	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%

First Author, Publication Year, Country	Strengths	Limitations
Engel et al., 2010[18] Germany	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
Vasen et al., 2010[19] The Netherlands	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The baseline characteristics of the patients included in the study were not fully described • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%

First Author, Publication Year, Country	Strengths	Limitations
Jarvinen et al., 2009[20] Finland	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The baseline characteristics of the patients included in the study were not described • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%
De Jong et al., 2006[21] The Netherlands	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%

First Author, Publication Year, Country	Strengths	Limitations
Dove-Edwin et al., 2006[22] UK and The Netherlands	*Reporting* • The objective was clearly described • The main outcome measures were clearly described • The baseline characteristics of the patients included in the study were described • Actual probability values were reported *Internal validity – confounding* • Patients in different intervention groups were recruited from the same population *External validity* • The participants were representative of the entire population from which they were recruited	*Reporting* • The characteristics of patients lost to follow-up were not described • Adverse events were not reported *Internal validity – bias* • Attempt was not made to blind those measuring the main outcomes of the intervention • Follow-up was not the same for all participants *Internal validity – confounding* • Patients in different intervention groups were not recruited over the same period of time • Patients were not randomized to intervention groups *Power* • A power calculation was not reported for the primary outcome • The study did not have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%

APPENDIX 4: Main Study Findings and Authors' Conclusions

First Author, Publication Year, Country	Condition / Interventions	Results
Health Technology assessment		
Bonis et al., 2007[14] USA	With surveillance vs without surveillance	• Statistically significant increase in survival (cumulative CRC-specific survival 10 years after surgery: 93% vs 68%) • Increase, but not statistically significant, in 5-year survival (87% vs 63%) • Increase, but not statistically significant, in overall survival (85% vs 62%) • Decrease, but not statistically significant, in CRC mortality (1/11 vs 108/238) • Statistically significant decrease in risk of endometrial cancer (0/61 vs 69/210) and risk of ovarian cancer (0/47 vs 12/223) • Statistically significant decrease in risk of developing extra-colonic cancer (0.5% vs 4.5%) • No difference in the risk of CRC (3.5% vs 3.8%)
Authors' conclusions: *"HNPCC family members who took subsequent actions or interventions had a lower risk of developing HNPCC-related cancers and lower mortality rates, compared to those who did not take actions."*[14] p.145		
Observational studies		
Ketabi et al., 2014[15] Denmark	Gynecologic surveillance of 2,959 at risk women for endometrial cancer (Once every 2 years from the age of 25 years) Mean time of surveillance: 6.5 years (range: 0.1 to 21.7 years) Lynch (n=676, 23%) vs AMS (n=892, 30%) vs AMS-like (n=1,391, 47%)	Incidence rate of endometrial cancer (cases per 100 women years): • Lynch = 0.63 • AMS = 0.06 • AMS-like = 0.05 Incidence rate ratio (95% CI): • Lynch = 10.7 (3.8, 30.8), p<0.0001 • AMS = 1 • AMS-like = 0.89 (0.22, 3.55), p=0.86 Median (range) age at diagnosis, years: • Lynch = 54 (39 to 83) • AMS = 65 (59 to 68) • AMS-like = 62 (55 to 73)
Authors' conclusions: *"the current biennial EC surveillance should only be targeted at MMR mutation carriers starting from the age of 35 to 40 years as the youngest age at diagnosis of EC in our study was 39 years."*[15] p.530		
Fu et al., 2013[16] China	Cancer surveillance of 263 members of 42 Lynch syndrome families Colonoscopy (Once in 1 to 2 years for mutation carriers and once in 5 years for non-mutation carriers from the age 20 years or over)	Incidence rate of CRC: • Carrier = 50.7% (73/144) • Non-carriers = 0% (0/119), p<0.01 Incidence rate of other cancer: • Carrier = 8.3% (12/144) • Non-carriers = 0% (0/119), p<0.01 Early cancer detected: • With surveillance = 70.0% (7/10) • Without surveillance = 36.5% (23/63), p<0.01

First Author, Publication Year, Country	Condition / Interventions	Results
	Surveillance period: May 2001 to October 2008 • Carriers (n=144, 55%) vs non-carriers (n=119, 45%) • Surveillance (n=180, 68%) vs non-surveillance (n=83, 32%)	Advanced cancer detected: • With surveillance = 30.0% (3/10) • Without surveillance = 63.5% (40/63), *p*<0.01
Authors' conclusions: *"MMR gene mutation carriers in Chinese Lynch syndrome families were found to be at substantially higher risk for the development of Lynch syndrome-related cancers as compared to non-mutation carriers…. In Lynch syndrome family members, we recommend pre-symptomatic MMR gene mutation analysis in order to identify high risk individuals for colonoscopy surveillance."*[16] p. 225 and p.230		
Stuckless et al., 2012[17] Canada	Colonoscopic surveillance 322 Lynch syndrome carriers (152 entered CRC screening program and 170 did not) Colonoscopy (every 1 to 2 years starting at age 20 to 25 years) Median follow-up: 9 years in males and 11 years in females (or to death) Surveillance (n=152, 47%) vs non-surveillance (n=170, 53%)	CRC risk (with vs without surveillance): • Males: RR (95% CI) = 0.29 (0.16 to 0.53) with median age being 58 years vs 41 years • Females: RR (95% CI) = 0.29 (0.16 to 0.53) with median age being 79 years vs 57 years Median survival (with vs without surveillance): • Males = 66 years vs 52 years (RR = 0.38; 95% CI 0.13 to 1.0) • Females = 80 years vs 63 years (RR = 0.19; 95% CI 0.085 to 0.44) CRC developed within 2 years of previous colonoscopy: • Males: 20% • Females: 7%
Authors' conclusions: *"Although colonoscopic screening was associated with decreased CRC risk and better survival, CRCs continued to occur. CRC development may be further reduced by decreasing the screening interval to 1 year and improving quality of colonoscopy."*[17] p.439		
Engel et al., 2010[18] Germany	Colonoscopic surveillance of 1,126 members (with or without history of CRC [CRC^{pos} vs CRC^{neg}]) of Lynch syndrome families: • MMR gene mutation (MUT) • No MMR mutation but with MSI (MSI) • Fulfill AMS criteria without MSI (MSS) Colonoscopy (once per year starting at age 25 years Observation time: 4,198	CRC risk (cumulative probability) at age 60 years in CRC^{neg} group: • MUT or MSI = 23.0%; 95% CI 14.8% to 31.2% • MSS = 1.8%; 95% CI 0.0% to 5.1% (*p*=0.01 compared with MUT and MSI) CRC risk (cumulative probability) at age 20 years in CRC^{pos} group: • MUT or MSI = 23.7%; 95% CI 14.5% to 32.9% • MSS = actual number not reported; risk was very low compared to MUT and MSI judging from the graph

First Author, Publication Year, Country	Condition / Interventions	Results
	person-years CRC^{pos} (N=724): MUT (n=378) vs MSI (n=271) vs MSS (n=72); 3 not tested CRC^{neg} (N=402) MUT (n=244) vs MSI (n=85) vs MSS (n=65); 8 not tested	
Authors' conclusions: *"Annual colonoscopic surveillance is recommended for individuals with HNPCC. Less intense surveillance might be appropriate for MSS families."*[18] p.174		
Vasen et al., 2010[19] The Netherlands	Colonoscopic surveillance of 745 mutation carriers of 205 Lynch syndrome families and 344 relatives of 46 non-Lynch syndrome families Colonoscopy (every 1 to 2 years starting at age 20 to 25 years) Mean follow-up: 7 years (range: 0 to 14.2 years) Mutation carriers (n=745) vs members of non-Lynch syndrome families (n=344)	Incidence rate of CRC: • Lynch = 4.4% (33/745); cumulative risk was 6% after the 10-year follow-up period • Non-Lynch = 1.7% (6/344), $p<0.05$ Incidence rate of extra-colonic cancers: • Lynch = 24.4% (182/745) • Non-Lynch = 8.7% (30/344), $p<0.001$
Authors' conclusions: *"With surveillance intervals of 1-2 years, members of families with Lynch syndrome have a lower risk of developing CRC than with surveillance intervals of 2-3 years. Because of the low risk of CRC in non-Lynch syndrome families, a less intensive surveillance protocol can be recommended."*[19] p.2300		
Jarvinen et al., 2009[20] Finland	Surveillance of 609 members (mutation positive and mutation negative) of 57 Lynch syndrome family Colonoscopy (max 3-year intervals) Transvaginal ultrasound (every 2 to 3 years starting at age of 35 years) Observation period: 11.5 years (or to death) 242 mutation positive (carriers) vs 367 mutation negative	Incidence rate of cancer (CRC and other cancers): • Mutation positive: 27% (65/242) • Mutation negative: 5% (17/367) Risk of cancer: • RR = 5.80; 95% CI 3.43 to 9.50; $p<0.00001$ Mortality rate: • Mutation positive: 6% (15/242) • Mutation negative: 5% (18/367) Risk of mortality: • RR = 1.26; 95% CI 0.65 to 2.46; $p=0.49$ Cancer-related deaths: • Mutation positive: 4% (9/242) • Mutation negative: 2% (6/367) Risk of cancer-related deaths: • RR = 2.28; 95% CI 0.82 to 6.31; $p=0.104$

First Author, Publication Year, Country	Condition / Interventions	Results
Authors' conclusions: *"Mutation carriers of Lynch syndrome have a clearly increased cancer risk despite adequate surveillance for CRC and EC. However, within a median follow-up time of 11 years, no significant increase in overall or cancer mortality was observed."*[20] p.4796		
De Jong et al., 2006[21] The Netherlands	Surveillance of 2,788 members of 140 Lynch syndrome families Colonoscopy (every 1 to 2 years starting at age of 20 to 25 years) Transvaginal ultrasound (every year starting at age of 30 to 35 years) Observation time: 92,196 person-years (from 1960 to 2004) Surveillance (n=897) vs Non surveillance (n=1073)	Standardized mortality ratio (SMR) = Observed/expected • Surveillance = 6.4 (14/2.2) • Non surveillance = 23.8 (200/8.4); *p*<0.001
Authors' conclusions: *"Since the introduction of surveillance, the mortality because of CRC has decreased."*[21] p.665		
Dove-Edwin et al., 2006[22] UK and The Netherlands	Colonoscopic surveillance of 91 relatives of 29 Lynch syndrome families and 197 relatives of 68 non-Lynch syndrome families Colonoscopy (at least 2 years starting at age 45 to 50 years) Observation period: 1987 to 2003 Lynch (n=91) vs non-Lynch (n=197)	Incidence rate of cancer: • Lynch = 4.4% (4/91) • Non-Lynch = 0.0% (0/197); *p*=0.010 Risk of adenomas: • Lynch = 7.7% (7/91) • Non-Lynch = 7.6% (15/197) • RR = 1.15; 95% CI 0.6 to 2.3
Authors' conclusions: *"Individuals with an autosomal dominant family history of colorectal cancer with and without evidence of Lynch syndrome are at equal risk of high-risk adenomas during surveillance, but colorectal cancer was only seen in Lynch syndrome. Therefore, non-lynch syndrome individuals do require colonoscopic surveillance, but the interval could be lengthened because risk of (interval) cancer is low. Lynch syndrome individuals require short surveillance intervals as is the recommended practice."*[22] p.1995		

AMS = Amsterdam I or II criteria; CI = confidence interval; CRC = colorectal cancer; EC = endometrial cancer; HNPCC = hereditary non-polyposis colorectal cancer; MMR = mismatch repair; MSI = microsatellite instability; RR = relative risk; TVUS = transvaginal ultrasound; vs = versus