EpidemiolPrev
supplemento 1
numero 2/3
anno 37
marzo
giugno
2013

e&p Quaderni

DETECTION OF THE INTERVAL CANCERS AND ESTIMATE OF THE SENSITIVITY OF COLORECTAL CANCER SCREENING PROGRAMMES

EDITOR: GISCoR Working GISCoR Working Group
"Interval cancers and sensitivity estimate"

WORKING REPORT

Gruppo italiano screening colorettale

Osservatorio nazionale screening

EDIZIONI inferenze

Inferenze Edizioni, via Ricciarelli 29, 20148 Milano. Poste Italiane spa - Sped. in abb. post. Dl. 353/2003 convertito in legge 27.02.04 n.46 - art.1, com.1, DCB Milano - Una copia 13,50 euro ISSN 1120-9763 marzo-giugno 2013

EPIDEMIOLOGIA & PREVENZIONE

Rivista fondata da Giulio A. Maccacaro

Anno 37 (2-3) 2013

Epidemiologia & Prevenzione
è indicizzata in Medline,
Science Citation Index Expanded,
Journal Citation Reports/Science Edition

Pubblicazione bimestrale Registrazione del Tribunale di Milano
n. 239/1977 Spedizione in AP - 45% - art. 2 comma 20b legge 662/96 - Milano.

Iscrizione al Registro degli Operatori di Comunicazione (ROC) n. 11747.

Una copia: 13,50 euro.

Abbonamento annuo: informazioni e condizioni sul sito www.epiprev.it

Gestione abbonamenti: ufficio abbonamenti
tel. 02 48702283, fax 02 48706089.

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IVA assolta dall'editore ai sensi dell'art. 74 lettera C del DPR 26/10/1972 n.633 e successive modificazioni e integrazioni nonché ai sensi del DM 29/12/1989. Non si rilasciano quindi fatture (art. 1 c. 5 DM 29/12/1989).

Testata associata
A.N.E.S.
ASSOCIAZIONE NAZIONALE EDITORIA PERIODICA SPECIALIZZATA

Stampa
Arti grafiche Ancora srl - Milano

EDIZIONI inferenze

via Ricciarelli 29, 20148 Milano
segreteria@inferenze.it

Direttore scientifico
Eugenio Paci

Vicedirettore scientifico
Francesco Forastiere

Past director
Benedetto Terracini

Direttore responsabile
Maria Luisa Clementi

Segreteria scientifica
Liliana Cori

Redazione
Marco Crespi, Cinzia Tromba

Segreteria di redazione
via Giusti 4, 21053 Castellanza (VA)
e-mail: epiprev@inferenze.it

Progetto grafico
Stefano Montagnana

Impaginazione
Giovanna Smiriglia

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Modalità di abbonamento
Pagamento con carta di credito (American Express, Carta Sì, VISA, Eurocard, Master Card) telefonando allo 02-48702283 dal lunedì al venerdì dalle 9 alle 13 oppure utilizzando il servizio PayPal sul sito web della rivista www.epiprev.it
Versamento su conto corrente postale n. 55195440 intestato a Inferenze scarl, via Ricciarelli n. 29, 20148 Milano (segnalare la causale del versamento).
Accredito tramite c/c bancario presso: UNIPOL BANCA P.za Wagner n. 8, 20145 Milano, IBAN: IT53P 03127 01600 000000003681 intestato all'impresa editoriale Inferenze scarl, via Ricciarelli n. 29, 20148 Milano.

Si ringrazia la Fondazione IRCCS Istituto nazionale dei tumori di Milano che ospita la Cooperativa.

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Detection of the interval cancers and estimate of the sensitivity of colorectal cancer screening programmes

Working report

Editor: GISCoR Working Group "Interval cancers and sensitivity estimate"

GISCoR Gruppo Italiano Screening ColoRettale

Gruppo italiano screening colorettale

OSSERVATORIO NAZIONALE SCREENING

Osservatorio nazionale screening

GISCoR Working Group
"Interval cancers and sensitivity estimate"

Coordinator

Manuel Zorzi, Padova

Corresponding author
Manuel Zorzi
Registro Tumori del Veneto
Passaggio Gaudenzio, 1
Padova
manuel.zorzi@ioveneto.it

Working Group

Bruno Andreoni, Milano
Emanuela Anghinoni, Mantova
Roberto Bardelli, Varese
Luigi Bisanti, Milano
Carlotta Buzzoni, Firenze
Cinzia Campari, Reggio Emilia
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[†] Dr. Ciatto died on May 4th, 2012

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anno 37 (2-3) marzo-giugno 2013

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Summary

Colorectal cancer (CRC) screening is aimed at reducing CRC specific mortality and, depending on the test adopted, CRC incidence. Many indicators are monitored in order to verify that this goal is achieved, under the assumption that if they meet given standards, it is reasonable to expect that mortality is reduced. One of the most important indicators is sensitivity, which can be measured using the interval cancers (ICs).
The Ministry of Health carries out an annual national survey on the results of the Italian colorectal screening programmes. The collection of ICs is beyond the objectives of that survey because it requires ad hoc surveillance systems.
The Italian Group for Colorectal Screening (GISCoR) publishes this Working Report on the collection of ICs and the estimate of sensitivity, with the purpose of easing and making homogeneous the monitoring of this fundamental aspect of screening programmes.
This Working Report describes how to detect the ICs using Hospital Discharge Records as the main source of information. The procedure to estimate the sensitivity of the screening programmes is based on the proportional incidence method. Finally, reference standards are proposed and suggestions for the interpretation of the results are given.

Keywords: colorectal cancer screening, interval cancer, screening sensitivity.

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Foreword

The primary target of colorectal cancer (CRC) screening is to reduce cause-specific mortality. It is difficult to measure this goal because it occurs with a latency of several years. Therefore, a number of early indicators are monitored, assuming that if precise standards are observed, then it is reasonable to expect a reduction in mortality.

It is clear, however, that, among all monitored parameters, the effectiveness of screening depends especially on the participation of the eligible population and on the proportion of diagnosed cancers (i.e., sensitivity). The latter can be measured through the detection of interval cancers (ICs).

DETECTION OF INTERVAL CANCERS (ICS) IS FUNDAMENTAL IN ORDER TO EVALUATE THE SENSITIVITTY OF SCREENING PROGRAMMES

In general, public opinion and the media consider ICs to be serious programme errors. Healthcare professionals fear this event, both for the impact on their professional image and for the legal and insurance implications. This aspect may be less important in colorectal screening, based on the fecal occult blood test (FOBT), than in mammography screening, at least as regards the first level of screening, given that the test is analyzed automatically in a laboratory. Instead, the problem can be important for all cases that undergo endoscopic assessment.

In fact, the detection of ICs is essential to highlight any organizational, technical, and professional limits in order to keep as low as possible the rates of false negatives, thus increasing the quality of the programme and, finally, its sensitivity.

Monitoring ICs is very important to evaluate and improve a programme's performance and also to confirm at a local level the scientific and biological assumptions that are the basis for the reduction of the disease-specific mortality.

We therefore provided professionals and programme organizers with a tool that, besides presenting some scientific/cultural references, may be of practical support for the detection of ICs and for estimating sensitivity.

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Colorectal cancer screening programmes

Colorectal screening programmes are progressively spreading all over Italy. According to the last survey by the National Centre for Screening Monitoring, by the end of 2009, 60% of Italians aged 50-69 years were residing in areas covered by organized screening programmes.[1] Overall, 2.9 million people were invited to screening and 1.4 million were tested in 2009.

The first level tests are FOBT (every 2 years) or flexible sigmoidoscopy – (once-in-a-lifetime) FS.

Most Italian programmes propose FOBT to the residents 50 to 69 years old. Few programmes instead propose FS to individual age cohorts (generally 58 yrs), or a combination of both tests.

Programmes based on FOBT use immunochemical tests on a single stool sample and without any dietary restriction. The test is quantitative and the positivity threshold is fixed at 100ng Hb/ml.

Subjects who test negative are advised by letter to repeat the test after two years. Subjects with a positive screening test are contacted to undergo a total colonoscopy (TC) or, when a complete colonoscopy is not possible, a double-contrast barium enema X-ray. The outcomes of second level assessment can be:

- negative: return to FOBT after 5 years
- cancer: further diagnostic assessment and therapy
- adenoma: endoscopic surveillance programme.

The monitoring of programmes activities is carried out through the regular collection of data and of process- and early-impact indicators.

The most important diagnostic indicators (test positivity rates, detection rates, positive predictive values) are strongly influenced by the frequency of the disease in the screened population. Both carcinoma and precancerous lesions are more common in males than in females and tend to grow steadily with age.[2] Moreover, the disease is expected to be more frequent at the first screening (prevalence round) than at subsequent ones (incidence rounds). Therefore, programmes collect specific data by screening episode (first and subsequent), sex and five-years age class.

AD HOC PROCEDURES
IN ORDER TO DETECT INTERVAL CANCERS PROCEDURES ARE NEEDED THAT ARE NOT AMONG THOSE ADOPTED IN THE CONDUCTION OF THE ONS ANNUAL SURVEY

The detection of ICs and their use for the evaluation of screening programmes sensitivity require *ad hoc* procedures that are beyond the scope of the annual survey conducted by the National Centre for Screening Monitoring.

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Interval cancers

DESCRIPTION OF THE PHENOMENON

Colorectal screening has been shown to be effective in reducing cause-specific mortality and, in Italy, it is currently recommended for the population aged 50 to 69 years.[3]

The effectiveness of screening is far from being absolute and the reduction of mortality reported in the FOBT-trials ranges between 12% and 19% according to the intention-to-treat analysis and up to 25% in the per-protocol analysis.[4] The trials used guaiac FOBT, whose sensitivity is significantly lower than the immunological FOBT that are used by Italian programmes.[5-9]

The results of two trials on FS-based programmes showed a reduction of incidence and mortality that lasts for more than 10 years: incidence was reduced by 18-23% (31-33% in the per-protocol analysis) and mortality by 22-31% (38-43%).[34,48]

A limit of the colorectal programmes is represented by a suboptimal sensitivity, with the proportion of ICs arising after a negative episode ranging from 38% to 63% in gFOBT studies[8-14] – except for the 4% registered in a yearly-based programme that used a set of 6 cards[15] – and from 18% to 33% in iFOBT studies.[8,9,16-18] In studies about FS programmes, the CRCs diagnosed after the screening episodes were 40% of those expected (20% if limited to the distal colon).These cases are defined as "interval cancers".

Compared to breast cancer screening, the knowledge of the biology of colorectal ICs is limited. Mammographic screening ICs do not seem to be different from the cancers diagnosed outside screening programmes as regards stage, grading. Also stage-specific survival is not different from that of clinical cancers.[19-21]

Information should be collected to verify whether ICs are more aggressive compared with clinical cancers, because they were not detected, were not bleeding when they were screened, or have particular morphological characteristics that make their identification difficult during colonoscopy.

ICs detected after a positive FOBT followed by a negative or incomplete colonoscopy or in subjects who did not attend a colonoscopy are particular cases that may have important practical implications concerning the preparation and quality of TC, communication with FOBT+ subjects, and a systematic use of sedation.

All ICs represent, in any case, a failure of screening programmes. For this reason, an analysis of ICs is highly recommended by European guidelines as a key aspect for the performance evaluation of screening programmes.[22]

DEFINITION AND CLASSIFICATION

ICs are primary colorectal cancers that are diagnosed after a complete and negative screening episode and either before the subsequent invitation to the programme or within a period corresponding to the screening interval (24 months for FOBT programmes). A screening episode should be considered negative also after the detection of non-invasive lesions (such as initial or advanced adenomas) after a complete colonoscopy.

For programmes that use once-in-a-life FS, a longer protection is as-

INTERVAL CANCERS ARE PRIMARY COLORECTAL CANCERS DIAGNOSED **AFTER** A COMPLETE AND NEGATIVE SCREENING EPISODE

sumed (at least 10 years). Therefore, all ICs arising within this interval should be considered. Those detected in the first 3-5 years after the screening episode represent a limit of the test's performance, while those arising afterwards may be helpful to evaluate the programme's protocol and/or interval.
In order to compare different case-series, the following are some additional considerations.

- **Cases arising after two years**: some FOBT programmes may invite subjects after an interval longer that 24 months. Therefore, some cancers may be diagnosed in the third interval year, before the subsequent invitation. Programmes whose interval is longer than 24 months should record also these ICs and utilize them to estimate the real sensitivity of the programme.
- **False negative assessment**: these cases will be considered ICs, to be attributed to a lack of the second level assessment and not to the first level test.
- **Planned early recalls**: cancers diagnosed at short-interval controls (e.g., after the removal of many polyps or because of unsatisfactory preparation) should be considered screen-detected. Cancers diagnosed before a planned control should be considered ICs.
- **Post-polypectomy surveillance**: cancers diagnosed during endoscopic surveillance after a clean colon should be considered screen-detected. Cancers diagnosed before a planned control should be considered ICs.
- **Follow-up of non-attendees**: cancers diagnosed during the interval in subjects who do not attend colonoscopy after a positive FOBT or who suspend it before its conclusion should not be regarded as ICs. The same applies to cancers diagnosed in subjects who did not attend the planned early recalls or the post-polypectomy surveillance.
- **Lapsed attendees**: cancers diagnosed in subjects who did not comply with the invitation to a subsequent screening should not be considered ICs.

DEFINITIONS FROM OTHER GUIDELINES

We have cited the definitions from other agencies in order to facilitate the comparison of different experiences.

- Manuale Indicatori GISCoR (2007)[23]

ICs are defined as colorectal primary tumors diagnosed after a screening episode (both first and second level) with a negative result for cancer and before the next invitation to programme or for people who have reached the upper age limit within a period of time equal to the period of invitation (24 months for FOBT programmes). For subjects undergoing endoscopy, both a first level FS and a second level TC, consider a 5-year interval period.

- English programme (2003)[24]

A cancer diagnosed not more than two years after a complete screening episode (i.e., in an individual who has a screening result available), that was not screen-detected. Note that this definition includes people who had further investigations recommended but did not have or did not complete them.

- European Guidelines (2010)[22]

Interval cancers are those that occur following a negative screening episode and in the interval before the next invitation to screening is due. For fecal occult blood testing, interval cancers may occur following a negative FOBT or following a positive test result with an additional negative assessment (colonoscopy).

The definitions given about planned early recalls, post-polypectomy surveillance, and follow-up of non-attendees also apply to FS screening programmes.
In conclusion, we can distinguish:

- ICs diagnosed after a negative FOBT test. They are used to estimate the sensitivity of the test and of the screening programme;
- ICs diagnosed after FOBT+ and false negative TC. They are used to estimate the sensitivity of the programme and to evaluate the second level assessment.

In practice

Not all cancers diagnosed after a screening episode should be considered ICs. To calculate the sensitivity of the screening programme, use the following scheme.
A NOTE OF CAUTION. There are many specific cases: refer to the classification in the previous page..

OUTCOME OF THE FOBT SCREENING EPISODE	DELAY	
	WITHIN 2 YEARS	OVER 2 YEARS
FOBT-	yes	no
FOBT+ TC-	yes	yes, only for TC[1]
FOBT+ not attending TC	no	no
FOBT+ incomplete, TC not repeated	no	no
FOBT+ TC+ (apart from cancer)[2]	yes	yes, only for TC3[3]
OUTCOME OF THE FS SCREENING EPISODE	**ONSET BEFORE 10 YEARS**	
FS-	yes	
FS+ TC-	yes, only for TC[1]	
FS+ not attending TC	no	
FS+ TC incomplete, TC not repeated	no	
FS+ TC+ (apart from cancer)[2]	yes, only for TC[3]	

Legend: FOBT = faecal occult blood test; TC = total colonoscopy; FS = flexible sigmoidoscopy
[1] within 5 years
[2] TC+ refers to a clean colon with the detection of adenomas (even advanced adenomas)
[3] with different intervals, according to the diagnosed lesion at TC. For instance, 3 years for intermediate and 5 years for low-risk adenomas.[22] Such IC should be used to evaluate the performance of TC and the appropriateness of follow-up protocols.

DETECTION OF INTERVAL CANCERS

ICs are diagnosed in subjects undergoing a diagnostic exam to evaluate some symptoms or signs arising after a negative screening episode. The diagnosis may take place outside the services of the local screening programme. Therefore, in order to detect all the ICs, a screening programme has to look for them actively. The safest and most complete instrument for detecting ICs are Cancer Registries (CR), whose use is recommended in the European Guidelines.[22] However, CRs are affected by some drawbacks that limit their use. First, many screening programmes are not covered by a CR. Second, most CRs make available their data with a gap of three or four years. Since CRC screening programmes are recent, it is important to expand the follow-up to evaluate their sensitivity as much as possible, up to the current period. For these reasons, it may be necessary to use other data sources.

In many programmes, Hospital Discharge Records (HDR) have been used. HDRs are an administrative tool and are, therefore available with a minimum lag. In Italy, also the HDRs of admissions to hospitals outside the region of residence are usually available within six months after discharge.

Table 1 shows ICD9 CM and DRG codes suggesting the presence of a diagnosis of ICs.

HDRs may be used following these steps:

1. extract from the screening archives a list of the screened subjects with a negative and complete screening episode and with the related episode date;

2. link this list with the HDR archives and select the CRC-related admissions that took place after the screening episode;

3. confirm the diagnosis by consulting different sources of information, such as pathology databases and medical records.

If the screening database does not allow the identification of subjects with a negative and complete screening episode, it is possible to subsequently extract the list of all the screened subjects and to exclude the screen-detected cancers and the cancers diagnosed after an incomplete episode.

The main limitation of HDRs is the possible loss of cases. In fact, initial forms of CRC (i.e., cancerised adenomas) can be treated exclusively by endoscopic removal in an outpatient setting, without any admission to hospital.

However this seems unlikely because the distribution by stage at the diagnosis of IC case series have shown a low proportion of cases at stage I. The possible loss of cases was studied by the Veneto Cancer Registry, which estimated the number of missed CRCs had HDRs been the only source of data.[18] Only 19 out of 1,405 CRCs registered in 2002-03 were missed, equal to 1.4%. This proportion does not seem to affect significantly the estimates of sensitivity and it is largely overcome by the advantages of using HDRs.

ICD9 CM CODE	DESCRIPTION
153	Malignant neoplasm of colon
154	Malignant neoplasm of rectum, rectosigmoid junction, and anus
2113	Benign neoplasm of colon
2114	Benign neoplasm of rectum and anal canal
2119	Benign neoplasm of other and unspecified site
2303	Carcinoma in situ of colon
2304	Carcinoma in situ of rectum
2309	Carcinoma in situ other and unspecified digestive organs
2352	Neoplasm of uncertain behaviour of stomach, colon and rectum
2355	Neoplasm of uncertain behaviour of other and unspecified digestive organs
V1005	Personal history of malignant neoplasm large intestine
V1006	Personal history of malignant neoplasm rectum, rectosigmoid junction, and anus
DRG CODE	**DESCRIPTION**
146	Rectal resection, with complications
147	Rectal resection, without complications
148	Major small & large bowel procedures, with complications
149	Major small & large bowel procedures, without complications
172	Digestive malignancy, with complications
173	Digestive malignancy, without complications

Table 1. Codes used to identify admissions with a possible diagnosis of colorectal carcinoma.

However, the proportion of stage I cancers might increase with a more widespread spontaneous use of TC during the post-screening interval, which are generally non-specific.
The database of outpatient exams (see **table 2**) could be helpful in identifying cases missed by HDRs. The procedures of interest are related to operative endoscopy (biopsy, polypectomy) and the subsequent pathologic examination.
It should be emphasized that this research can lead to the extraction of large numbers of suspect exams whose evaluation requires a direct access to pathology datasets.
It is important to define precisely the incidence date of identified cancers, in particular when the diagnosis takes place around the end of the second year of follow-up. Here are the Italian Cancer Registries Association rules.[25] Take in consideration, in decreasing order:
a. the date of the first histological or cytologic diagnosis of cancer. Refer to the date of acceptance of sampling in the Pathology Service;
b. the date of admission to hospital when the first diagnosis of cancer took place;
c. outside admission to hospital: the date of first clinical or instrumental exam when the first diagnosis of cancer took place;
d. dates other than a, b, or c.

DESCRIPTION
Total colonoscopy with flexible endoscope
Sigmoidoscopy with flexible endoscope
Endoscopic biopsy of small intestine
Endoscopic biopsy of large intestine
Endoscopic polypectomy of large intestine
Endoscopic biopsy of rectum
Endoscopic polypectomy of rectum

Table 2. Outpatient exams possibly associated with CRC.

In practice

To detect ICs, HDRs can be used to:
- produce a list of screened subjects with a negative and complete screening episode, including the date of the episode;
- link it with HDR archives and make a list of 'suspect' admissions to hospital (according to the codes in table 1);
- confirm the diagnosis using the pathology archives and/or medical records.

If the screened subjects with a negative and complete episode of screening cannot be selected, extract all the screened subjects, excluding screen-detected cancers and cases diagnosed after an incomplete screening episode at a later time.
The database of outpatient exams could be helpful in identifying cases missed by HDRs.

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Methods to estimate sensitivity

ICs can be considered as false negative episodes and, as such, they may be used to estimate sensitivity. Among the different definitions of sensitivity that have been proposed, we will refer to the sensitivity of the screening programme that measures the diagnostic ability of the screening test and of the second level assessment altogether, and the sensitivity of the screening test.[a]

One method to estimate sensitivity is suggested in the European Guidelines for Breast Cancer Screening[26] and calculates sensitivity as the screen-detected cancers divided by all the cancers diagnosed in a screened population, i.e., the screen-detected plus the ICs.[b]

This method is affected by some biases. First, it compares ICs that, by definition, may occur during the two-year interval, with the screen-detected cancers that could arise in a much longer period because screening could yield a longer diagnostic anticipation. This method is also affected by length bias and over-diagnosis. In brief, it overestimates sensitivity, in particular during the prevalence round of a screening programme.

The proportional incidence method, that has been recommended by the European guidelines for colorectal cancer screening,[22] is free from these biases.[27] This method measures screening sensitivity in terms of a reduction of cancer occurrence in the screened population during the interval. It compares the incidence of ICs with the incidence that would be expected in the absence of the screening episode, i.e., the underlying incidence observed in the population. The observed/expected cases ratio is called proportional incidence.[c] The closer the observed cases are to those expected, the less efficient the screening episode, i.e., the lower its sensitivity. Conversely, in a hypothetical screening with a sensitivity of 100%, no ICs would occur and the proportional incidence would be equal to zero.

The proportional incidence is usually measured for the entire interval as well as separately for each interval year. For FS programmes, it should be measured at least every two years up to the tenth year after the screening episode.

All analyses should be stratified or adjusted by age and sex and, for FOBT programmes, by first *vs* subsequent screening episodes.

The most important drawback of the proportional incidence method is the possible difficulty in estimating the underlying incidence in the absence of screening.

[a] In fact, according to Hakama,[28] programme sensitivity is the proportion of all cancers occurring in a population who are diagnosed by screening. It is a measure of the impact of the screening programmes that is behind the purposes of this manual. What we refer to as 'programme sensitivity' is defined by Hakama as 'episode sensitivity'.

[b] Example: a screening programme detects 300 cancers, while 80 ICs occur during the two-year interval. Sensitivity = 300/(300+80) = 79%. Interpretation: the screening programme identified 79% of the cases.

[c] Example: 30 ICs occur during the first year after the screening episode and another 50 ICs in the second year. In the screened population, 100 incident cases were expected during the first year and 100 in the second year. The proportional incidence is (30+50)/(100+100) = 0.4. Interpretation: The screening programme did not anticipate the diagnosis of 40% of the cancers that would have occurred without it; therefore, its sensitivity was equal to 60% (1-0.4 or 100%-40%).

In practice

To estimate sensitivity, use the proportional incidence method that compares the number of ICs with the CRCs that would be expected in the screened cohort in the absence of screening.

Do not use the method that divides screen-detected cases by the sum of screen-detected plus interval cancers as it is affected by distortions that overestimate sensitivity.

THE PROPORTIONAL INCIDENCE METHOD

To calculate the proportional incidence, the following data are needed:

- underlying incidence rate (in the absence of screening);
- follow-up person-years of the screened cohort in the first and second interval year;
- number of ICs in the screened cohort in the first and second interval year.

Sex and age-specific data should be available to allow a more accurate estimate of the proportional incidence and sensitivity.

Estimating the underlying incidence rate

The incidence rates in absence of screening may be provided by the local Cancer Registry (CR), referring to the period immediately before the start of the screening programme.

If, during the period before screening, a trend in incidence rates is observed, adjusted incidence rates should be used to calculate the expected CRCs.

The screening programmes of areas not covered by a CR can use incidence data from nearby areas or from their geographic macro-area. It is better to use five-year age- and gender-specific incidence data. **Tables 3 and 4** (pg 14) show the overall and specific incidence rates by age and gender of the four Italian macro-areas in 1998-2002, with the incidence trend expressed as Annual Percent Change (APC) calculated over the period 1995-2002.

To adjust the expected incidence rates by the trend, the incidence rate can be applied to the APC for each year elapsed between the last year of the period on which it was produced and (for simplicity) the middle year of the period of collection of ICs, according to the formula:

$$adjusted\ incidence\ rate = t \times (1 + APC)^n$$

where: t = incidence rate,
APC = annual percent change
n = number of years[a]

[a] Example: a screening programme collected ICs during the years 2007-2009. The incidence rate in 1999-2002 was 120 x 100,000 with an APC of +0.9%. The trend has to be applied for 6 years (from 2003 to 2008) and the adjusted incidence rate is 120 x $(1+0.009)^6$ = 126.63.

MACRO-AREA	MALES		FEMALES	
	incidence rate	APC	incidence rate	APC
North West	150.9	0.7	99.5	0.5
North East	156.8	0.6	96.7	0.9*
Central	160.3	0.3	99.9	-0.4
South and Islands	101.0	1.7	73.0	3.2*
* statistically significant				

Table 3. Incidence rates (x 100,000) in 1998-2002 and Annual Percent Change (APC) (period 1995-2002) in subjects aged 50 to 69, by sex and macro-area. Source: AIRTUM.

AGE (YEARS)	NORTH WEST		NORTH EAST	
	males	females	males	females
50-54	63.9	51.0	68.4	52.1
55-59	115.1	83.6	119.2	86.8
60-64	178.0	107.0	186.5	107.9
65-69	265.9	158.9	285.3	147.0
70-71	345.6	186.7	372.0	183.8
AGE (YEARS)	**CENTRAL**		**SOUTH AND ISLANDS**	
	males	females	males	females
50-54	71.7	54.0	49.3	40.1
55-59	120.9	74.7	69.3	53.9
60-64	194.6	112.4	120.0	86.6
65-69	277.9	165.7	188.0	118.2
70-71	351.0	209.8	235.6	143.0

Table 4. Incidence rates (x 100,000) in 1998-2002 by age, sex and macro-area. Source: AIRTUM.

In practice

The underlying incidence rates can be estimated using the data from the local Cancer Registry or those of the macro-area.

Refer to the incidence rates of the period immediately before the start of the screening programme.

If a trend has been observed, use it to adjust the incidence rates.

Follow-up of the screened cohort

To calculate the proportional incidence, it is necessary to identify the cohort of subjects with a negative and complete episode of screening and to quantify its person-years of follow up.

It is necessary to extract from the screening archives a list of subjects with a complete and negative screening episode, including the date of the screening test.

Each subject will contribute to the overall person-years of follow-up starting from the date of each screening test (there may be more than one if the study period is longer than two years), up to one of the following:

1. diagnosis of CRC;
2. death;
3. emigration;
4. end of the follow-up;
5. reaching the 730th day;
6. next screening episode, from which a new count starts.

The frequency of the first three events is almost negligible; therefore, it is reasonable to detect only the last three.

It is important to distinguish the first year of interval from the second. The first 365 days of following-up each subject are attributed to the first interval-year, with the following days, up to the 730th, to the second interval-year.[a]

Another aspect must not be forgotten. During the interval, the onset of ICs is not constant, but it progressively increases over time after the screening episode. Therefore, for instance, a person-year deriving from the sum of one month of follow-ups for 12 subjects is not comparable to that given by 12 months of follow-up for a single individual: in the first case, the risk of disease is much lower. For this reason, follow-up periods shorter than 365 days should be excluded from the overall person-years of the first interval year and periods shorter than an additional 365 days from the second.

It is important to build specific cohorts by sex, age and, for the FOBT programmes, screening episode (first vs subsequent). In fact, the screened population is not homogeneously distributed, with a prevalence higher among women and among subjects in the intermediate age group (between 55 and 64 years).[29] A table like the following should be produced.

AGE (YEARS)	FIRST YEAR OF INTERVAL		SECOND YEAR OF INTERVAL	
	male	female	male	female
50-54	33,100	35,858	32,402	35,160
55-59	35,684	38,658	34,987	37,961
60-64	32,896	35,638	32,198	34,940
65-69	26,849	29,086	26,152	28,389

Table 5. Person-years of follow-up.

The follow-up of the subjects who underwent a second level TC depends on the specific recommendation established for surveillance (for instance, 3 years for intermediate-risk adenomas and 5 years for low-risk adenomas[22]).

Before describing how to estimate the expected CRCs, we will discuss how to deal with another aspect in the next chapter.

[a] Example: a subject with a follow-up of 400 days will contribute to one person-year for the first year of interval, while the 35 days left over will not be used for the second year.

In practice

To calculate the person-years of follow-up of the screened cohort, a list has to be produced, first of all, of the subjects with a negative and complete screening episode, including the date of screening test. Each subject will contribute to the overall person-years of follow-up from the date of screening up to one of the following:

- diagnosis of CRC, death, emigration (infrequent);
- end of the follow-up;
- reaching the 730th day;
- next screening episode, from which a new count starts.

Assign the first 365 days of follow-up of each subject to the first year of interval and the following days, up to the 730th, to the second. Follow-up periods shorter than 365 days should be excluded from the overall person-years of the first interval year and periods shorter than an additional 365 days from the second.

Adjustment for aging of the screened cohort

During the interval, screened subjects grow older. This fact should be taken in account to calculate the expected number of cases arising in the screened cohort using the underlying incidence, to avoid underestimating sensitivity.

If individual file records, including birth date, of the screened subjects are available the adjustment for aging can be carried out assigning each subject to the correct five-year age group for each of the two intervening years.

Otherwise, the adjustment can be made as follows.

The screened cohort is usually split into five-year age groups. During the first interval year, the subjects in last year of each age group (e.g., the 54-year-olds in the 50-54 age group) grow older and they should enter the older age group. It is reasonable to assume that these subjects contribute with half of their first year of follow up to their class of origin and with the other half to the older class. The other subjects (those 50-53 years old) spend the whole year in the original age group.

During the second interval year, all of those screened grow older by another year, so that the remaining half of the 54-year-old subjects and the 53-year-olds should enter the older age group.

Now, assuming that the age distribution of the screened subjects is homogeneous within each age group (i.e. the 54-year-old subjects are 1/5 of the 50-54 year cohort), half of those screened in the last year of that age group (half of 1/5, i.e. 1/10) will move to the older age group during the first interval year (**table 6**, pg 17).

During the second interval year, the remaining half of the 54-year-old subjects and half of the 53-year-olds should enter the older class (i.e., the second half of the 54-year-old subjects and half of the 53-year-olds, equal to 1/10 + 1/10 = 1/5). The adjusted person-years of follow-up is exemplified in **table 7**.

In our example, we had 710 expected cases compared to 654 cases without adjusting for aging. Given the 151 IC found, the adjusted sensitivity was 78.7, the non-adjusted was 76.9.

FIRST INTERVAL YEAR						
age	screened	remained (9/10)	moved (1/10)	adjusted person-years of follow-up	incidence (x 100,000)	expected cases (person-years x incidence)
50-54	68,958	62,062	6,896	62,062	59.5	36.9
55-59	74,342	66,908	7,434	66,908 + 6,896	98.7	72.8
60-64	68,534	61,681	6,853	61,681 + 7,434	144.8	100.1
65-69	55,935	50,342	5,594	50,342 + 6,853	203.1	116.2
70-71				5,594	270.9	15.2

Table 6. Adjustment for aging of the screened cohort in the first interval year.

SECOND INTERVAL YEAR						
age	screened	remained (7/10)	moved (1/10+1/5)	adjusted person-years of follow-up	incidence (x 100,000)	expected cases (person-years x incidence)
50-54	68,958	48,271	20,687	48,271	59.5	28.7
55-59	74,342	52,039	22,303	52,039 + 20,687	98.7	71.8
60-64	68,534	47,974	20,560	47,974 + 22,303	144.8	101.8
65-69	55,935	39,155	16,781	39,155 + 20,560	203.1	121.3
70-71				16,781	270.9	45.5

Table 7. Adjustment for aging of the screened cohort in the second interval year.

In practice

To adjust the screened cohort for aging, the distribution of the screened subjects within age classes is assumed to be homogeneous and the person-years of follow-up adjusted as follows:

- first interval year: move 1/10 of each age group to the next;
- second interval year: move 3/10 of each age group to the next.

Estimating the number of expected colorectal cancers

The incidence rates are much different between sexes and age groups; therefore, the sex and age-specific number of expected CRCs should be calculated and then added to obtain the overall estimate. This step also permits evaluating sex- and age-specific sensitivity.

The calculation should be carried out separately for the first and the second interval year and, for FOBT programmes, by screening episode.

The expected number of CRCs is calculated by applying the incidence rate (eventually adjusted by a previous trend) to the person-years of follow-up of the screened cohort. The formula is:

$$expected\ CRCs = \frac{incidence\ rate \times person\ years\ of\ follow\text{-}up}{100{,}000}$$

A table like the following may be produced that, for simplicity, does not present the data by sex and screening episode.

AGE (YEARS)	INCIDENCE RATE* x 100,000	FIRST INTERVAL YEAR		SECOND INTERVAL YEAR	
		person-years of follow-up	number of expected CRCs	person-years of follow-up	number of expected CRCs
50-54	59.5	62,062	36.9	48,271	28.7
55-59	98.7	73,804	72.8	72,726	71.8
60-64	144.8	69,115	100.1	70,277	101.8
65-69	203.1	57,195	116.2	59,715	121.3
70-71	270.9	5,594	15.2	16,781	45.5

* incidence rates recorded by the Venetian Cancer Registry in 1999-2002.

Table 8. Calculation of the expected CRCs by age and interval year.

A note of caution. Do not calculate the total number of expected CRCs by multiplying the average 50-69 years incidence rate by the total person-years, instead add the sex- and age-specific numbers of expected CRCs.

In practice

The expected number of CRCs can be calculated by multiplying the sex- and age-specific number of person-years of follow-up of the screened cohort by the related incidence rates observed in the absence of screening.

The total number of CRCs will be the sum of the sex- and age-specific estimates.

Carry out separate calculations for the first and the second interval year.

Calculating the proportional incidence

The proportional incidence is the ratio between observed ICs and expected CRCs.
The formula is:

$$proportional\ incidence = \frac{observed\ ICs}{expected\ CRCs}$$

The computation should be performed separately for each interval year. It is also important to calculate the specific proportional incidence by age and sex and, for FOBT programmes, by screening episode.

Table 9 (pg 19) shows the calculation of the proportional incidence in the example of the previous chapters.

AGE (YEARS)	INCIDENCE RATE (x 100,000)	FIRST INTERVAL YEAR				SECOND INTERVAL YEAR			
		person-years of follow-up	number of expected CRCs	number of observed ICs	propor.-tional incidence	person-years of follow-up	number of expected CRCs	number of observed ICs	propor-tional incidence
50-54	59.5	62,062	36.9	12	32.5	48,271	28.7	11	38.3
55-59	98.7	73,804	72.8	10	13.7	72,726	71.8	21	29.2
60-64	144.8	69,115	100.1	10	10.0	70,277	101.8	20	19.6
65-69	203.1	57,195	116.2	16	13.8	59,715	121.3	36	29.7
70-71	270.9	5,594	15.2	2	13.2	16,781	45.5	13	28.6
Total	-	-	341.2	50	14.7	-	369.0	101	27.4

Table 9. Calculation of the proportional incidence, by age and interval year.

In practice

The proportional incidence is the ratio between observed ICs and expected CRCs.
Calculate the proportional incidence overall and for each interval year.
It is interesting to also calculate the specific proportional incidence by age and sex and, for FOBT programmes, by screening episode (first vs subsequent).

ESTIMATING SENSITIVITY

Sensitivity is defined as the complement to one of the ratio between observed ICs and expected CRCs (i.e., 1 – that ratio). The total programme sensitivity can be calculated using the following formula:

$$sensitivity = \left(1 - \frac{observed\ ICs_{first\ year} + observed\ ICs_{second\ year}}{expected\ CRCs_{first\ year} + expected\ CRCs_{second\ year}}\right) \times 100$$

Here is the calculation of sensitivity for the example in the previous chapters.

	FIRST INTERVAL YEAR		SECOND INTERVAL YEAR	
	number of expected CRCs	number of observed ICs	number of expected CRCs	number of observed ICs
Total	341.2	50	369.0	101

Sensitivity
= [1- (50 + 101) / (341.2 + 369.0)] x 100
= [1 - (151 / 710.2)] x 100
= [1 - 0.213] x 100
= 0.787 x 100 = 78.7%

Obviously, it is possible to calculate the specific sensitivity by age and sex and, for FOBT programmes, by screening episode (first vs subsequent).
To calculate programme sensitivity, ICs diagnosed after both a negative screening test and after a negative assessment session are utilized. As suggested by Hakama, expected CRCs should be calculated using the person-year of follow-up of both groups of subjects.[28]

A note of caution. To estimate overall programme sensitivity, the following formula has been proposed:

$$sensitivity = \frac{(proportional\ incidence_{first\ year} + proportional\ incidence_{second\ year})}{200}$$

This formula is correct only when the first and the second year of interval contribute equally to the overall follow-up, that is, when the person-years of follow-up of the two years are identical. In fact, the person-years of the first year are almost invariably greater.

In practice

Sensitivity is calculated as 1 – the ratio between observed ICs and expected CRCs.
To calculate programme sensitivity, use all the observed ICs, both those after a negative screening test and after a negative TC.
To calculate the test sensitivity, use only the ICs after a negative screening test.

ESTIMATING THE CONFIDENCE INTERVAL

It may be useful to calculate the confidence interval of sensitivity, in particular when preparing a paper for publication. They may be based on the normal distribution and on the exact Poisson distribution.[30]
The formulas are as follows:

$$upper\ interval = \left\{1 - \left[\left(1 - \frac{1}{9 \times IC} - \frac{1.96}{3 \times \sqrt{ICs}}\right)^2 \times \frac{ICs}{CRCs}\right]\right\} \times 100$$

$$lower\ interval = \left\{1 - \left[\left(1 - \frac{1}{9 \times (ICs + 1)} + \frac{1.96}{3 \times \sqrt{ICs + 1}}\right)^2 \times \frac{ICs}{CRCs}\right]\right\} \times 100$$

where:

ICs is the number of observed ICs
CRCs is the number of expected CRCs.

ADJUSTMENT FOR SELECTION BIAS

Some studies have reported higher levels of compliance to invitation in population groups characterized by a greater awareness of their health. This attitude could be associated both with a greater atten-

tion to symptoms and signs of possible diseases and the earlier uptake of diagnostic tests, but also with a healthier lifestyle in terms of diet, physical activity, or not smoking.[31,32]
Therefore, it is possible that the screened population is at lower risk of CRC than the general population and it would be inappropriate to use the general underlying incidence rates to estimate the expected CRCs in the screened population (selection bias). The latter would be overestimated, leading to an artificial increase of sensitivity.
Different methods have been proposed to adjust for selection bias. Hakama suggests introducing in the proportional incidence formula a factor related to the specific incidence observed in the non-compliers to screening.[28]
This data is available only from the cancer registries. Programmes without a CR can utilize the incidence rates observed in nearby areas that registered similar levels of compliance.
First, it is necessary to identify the subjects who were not invited to screening and those who did not comply with the invitation. It would be appropriate to verify whether the non-invited subjects were resident at the date of start of the study period of ICs.
This cohort should then be matched with the local CR in order to identify the incident CRCs and calculate the incidence rates.
The sensitivity estimate is adjusted for selection bias according to the following formula:

$$sensitivity = \left\{1 - \frac{(a \times I_{screen})}{[I_{under} - ((I - a) \times I_{non\text{-}screen})]}\right\} \times 100$$

where:

a is compliance to invitation
I_{under} is the underlying incidence rate in the absence of screening
I_{screen} is the incidence rate of IC in the screened population
$I_{non\text{-}screen}$ is the incidence rate of CRC in the non-invited and the non-compliers with the invitation

Using the previous example, given the following values:

Compliance to invitation (a) = 0.67
Underlying incidence rate (I_{under}) = 121.4
Incidence rate of IC in the screened (I_{screen}) = 28.2
Incidence rate in the non-screened ($I_{non\text{-}screen}$) = 139.7

The adjusted sensitivity is:

= {1 – (0.67 x 28.2) / [121.4 – (1– 0.67) x 139.7]} x 100
= {1 – 18.9 / [121.4 – (0.33 x 139.7)]} x 100
= {1 – 18.9 / [121.4 – 46.1]} x 100
= {1 – 18.9 / 75.3} x 100
= {1 – 0.251} x 100
= 0.749 x 100 = 74.9%

In practice

To adjust for selection bias:

- a local CR is necessary;
- identify the cohort of - non-screened individuals;
- link this cohort with the CR archive to identify the CRC cases diagnosed in the period of interest;
- calculate the person-years of the non-screened cohort;
- calculate the incidence rate in the non-screened cohort with the formula:

number of CRCs / person-years x 100,000

- adjust the sensitivity estimate using the following formula:

$$sensitivity = \left\{ 1 - \frac{(a \times I_{screen})}{[I_{under} - ((I - a) \times I_{non\text{-}screen})]} \right\} \times 100$$

STANDARDS

Currently no standards are available for proportional incidence and sensitivity. To identify proper standards, it is necessary to gather a large number of sensitivity estimates from different programmes. In the meantime, some reference values may be useful. The European guidelines for quality assurance in breast cancer screening and diagnosis have set the standards for proportional incidence at <30% for the first year after the screening episode and <50% for the second.[26]

The available data of sensitivity estimates from Italian FOBT programmes have showed better performances (**table 10**).

Therefore, we propose the following standards for the proportional incidence: <20% for the first year, <40% for the second.

FS programmes are also lacking standards derived from experimental studies or from population programmes. The available indications are built on case-control studies, that, 10 years after a negative endoscopy, showed a 74% reduction in the cancer incidence for the distal colon, compared to controls.[33] Even if the analysis has not yet been published regarding the CRC incidence in screened subjects with

PROGRAMME	PROPORTIONAL INCIDENCE		SENSITIVITY	95% CONFIDENCE INTERVAL
	First year	Second year		
Florence 1992-97 RPHA Test [9]	11.5	23.9	82.4	67 – 92
Florence 2000-02 Latex Test [17]	19.3	40.8	71.5	55.0 – 83.1
Veneto[18]				
Alto Vicentino	14.2	38.5	75.8	63.7 – 84.7
Bussolengo	15.5	29.5	79.0	67.5 – 87.2
Dolo	15.0	26.2	80.0	71.2 – 86.6
Feltre	23.3	45.4	67.0	45.5 – 81.5
Pieve di Soligo	14.0	28.4	79.6	72.1 – 85.5
Reggio Emilia[16]	16.8	43.0	70.9	61.5 – 78.5

Table 10. Proportional incidence and sensitivity of FOBT Italian programmes.

a negative test in the English trial, the 11-year follow-up showed a reduction by more than half of CRC incidence.[34,48]

Preliminary follow-up data of an Italian study comparing FS with FOBT showed a proportional incidence of CRC of 27% after 6 years of follow-up in subjects with a negative FS.[35]

Therefore, we propose using the value of <40% as a standard for proportional incidence in the 10 years after a negative endoscopy.

Further analysis of current studies will permit defining this standard more precisely, regarding both the interval and the anatomic site (the reduction of incidence is higher for rectal cancers – more than 80% – than for other sites, but no data are available yet to identify specific standards for proximal and distal colon).

In practice

Currently no standards are available.

It may be useful to refer to the following standards for the proportional incidence:

for **FOBT programmes**:

- <20% for the first interval year
- <40% for the second interval year

for **FS programmes**:

- <40% after 10 years of follow-up

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Interpretation of results

The different sensitivities allow an evaluation of many aspects of screening programmes.
A lower than expected test sensitivity will be associated only with the first level of screening. Regarding FOBT programmes, different aspects should be evaluated:

- type of test used;
- calibration of equipment;
- positivity threshold used (typically 100 ng/ml);
- sample management: delay between stool collection and laboratory analysis, exposure to high temperature, etc.

The possibility of errors in the recording of test results should also be considered.
In the subjects who underwent repeated negative screening episodes, it is reasonable to expect a reduction of ICs, with higher values of sensitivity. It could otherwise be concluded that ICs have some features that make them non-diagnosable by screening: they never bleed, grow at a very fast speed, are flat, or different combinations of the above.
For FS programmes, the specific sensitivity by anatomical subsite, both for distal and proximal colon, is particularly interesting.
A lower than expected test sensitivity could be associated with:

- the proportion of FS with inadequate and incomplete preparation;
- operators' experience, both at first and second levels;
- the positivity threshold used.

These items also apply to ICs identified after a second level TC.
The data about the TC that obtained a clean colon should be collected.
The adequacy of the screening interval can be evaluated through the specific sensitivity by interval year, especially in the second year after a negative FOBT, while, after a negative FS, it is important to estimate the sensitivity for up to ten years. The ICs diagnosed during the first years (3-5) represent a limit of the test's performance, compared to those arising afterwards, which may be helpful in then evaluating programme's protocol and/or interval.
Other elements to evaluate are the anatomic subsite - a higher prevalence of proximal cases can be expected - and the relationship with non-invasive lesions diagnosed at TC. In the latter case, remember that cancers diagnosed during endoscopic surveillance after a clean colon should be considered screen-detected because the assessment session should be able to prevent them.
We recommend that ICs be subject to a structured audit involving the monitoring service of the screening programme, laboratory, endoscopy as well as pathology and surgery.[36] Sensitivity results should be compared with such other indicators of the diagnostic performance of the programme as the positivity rate of FOBT or the adenoma detection rate of FS. The factors that may influence the results (i.e., the underlying incidence rates, the distribution by age and sex of the screenees as well as the proportion of complete FS) should be accounted for.
The type of IC should be analysed (mucinous, presence of attenuated polyposis, etc.)[37] as well as the

presence of hereditary syndromes in the patients; previous findings regarding the onset site of should be reviewed (previous large polyp or pT1 cancer treated only endoscopically).
Finally, ICs may be useful to complete the evaluation of the quality of endoscopy, which is usually measured through completion rate, withdrawal time, number of procedures per operator, and detection rate of adenomas that have been associated with the risk of IC.[38]
Monitoring specific sensitivity by the endoscopy service as a whole and by the individual endoscopist can provide useful indications to improve the endoscopy practice in screening.
the sensitivity trend in different periods can also highlight the impact of changes of first level protocols, second level equipment, the endoscopist's experience, etc. Finally, a comparison of results with other programmes may be informative too.

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Other data of interest

The main objective of the IC collection is to evaluate sensitivity. However, it is worth recording as much data as possible on ICs, which are a valuable source of information both for the evaluation of screening programmes and for research purposes.

NEGATIVE SCREENING EPISODE

It is important to collect the following data relative to the negative screening episode preceding each IC.

First level (FOBT programmes):

- test result and, if available, quantitative result (both negative and positive);
- screening episode (first, second,…).

First level (FS programmes):

- site and features of any lesions identified by FS;
- quality of bowel preparation;
- site reached by FS;
- endoscopist and endoscopy service codes.

Second level TC:

- completeness of the exam (incomplete TC, suboptimal visualization, further assessment using TC or barium enema X-ray, …);
- site and characteristics of any lesions identified by TC;
- endoscopist and endoscopy service codes.

To evaluate the specific sensitivity by endoscopist and endoscopy service, it is also appropriate to collect data about other quality indicators of endoscopy, such as completion rate, withdrawal time, number of procedures per operator, and detection rate of adenomas.

STAGE AT DIAGNOSIS

European guidelines for quality assurance in breast cancer screening and diagnosis recommend collecting the IC stage at diagnosis and comparing it to that of screen-detected cases and cases diagnosed in non-responders.[26]

We recommended collecting the stage at diagnosis of all ICs as it permits estimating length bias and the degree to which screening effectiveness is affected by ICs. It should be underlined that a complete collection of this data as well as of the baseline incidence rates by stage, require a detailed source of information, such as a local CR.

The most widely used classification is the clinical stage (TNM), which accounts for the fact that, even if most CRCs are treated by surgery, some of them undergo pre-operative radio- or chemotherapy, which

can obviously affect the stage. Unfortunately, the clinical stage is not always defined precisely and its definition is also affected by variable diagnostic protocols. In the absence of a local CR, the stage can be deduced from the pathological stage (TNM or Dukes) in the local pathology archives, linked with the information on eventual pre-operative therapy.
An approximate but useful classification distinguishes cancer as advanced (UICC III or more) or early. The histological report (state of the lymph nodes) is often enough for this purpose. Only cases with negative lymph nodes will require the two extra imaging exam reports (chest and upper abdomen).

SEASON

It has been reported that in the summer the FOBT positivity rates are lower than in other.[39] In fact, heat can modify the hemoglobin structure undermining the reliability of the immunochemical FOBT. This could cause an increase in false negative tests. However, published data on season-specific IC rates have shown a very high sensitivity of tests performed in the winter (88.2%) and a satisfactory sensitivity in the summer (78.5%).[40]
It could be appropriate to calculate the season-specific sensitivity as the range of temperature across the different Italian areas is quite wide.
For this purpose, screenees should be classified according to the season in which they have been tested, building season-specific cohorts of follow-up. Similarly, every IC should be attributed to the season when the negative screening episode took place.
Obviously, sensitivity estimates could also be carried out on a monthly basis; however, this increases the complexity of the analysis and, most importantly, it seriously reduces the number of events for each period, with a loss of statistical power.

ANATOMICAL SITE

This is of most interest for FS programmes that are expected to have a much higher sensitivity for the distal colon, which is directly visualized during the first level exam.
It is interesting to also evaluate the IC anatomical site for FOBT programmes in order to verify whether FOBT sensitivity is lower for proximal lesions, as reported in the literature,[41-45] as well as possible TC limits on the proximal colon.[46]
Again, the site-specific incidence rates can be made available only by a local CR.

BIOLOGICAL PROFILE

There are many markers of the biological profile of CRCs, but probably histotype and grading are more utilized than other more recent ones, such as KI67 or MSI.[47] The grading is affected by limitations in the inter-observer agreement but, with the purpose of local comparisons where both screen-detected cancers and ICs are evaluated by the same team of pathologists, this bias could be less relevant.
Generally, the most reliable information is derived from a biopsy because any pre-operative treatment can modify the grading, even if some differences between the biopsy grading and the surgical specimen were observed in cases with primary surgical treatment. If possible, it would be appropriate to collect both data and information on any pre-operative treatment.
More specific profiling involving molecular analysis may require ad hoc studies.

PRIMARY TREATMENT

It is appropriate to collect information on the type of primary therapy in order to fully understand the biological characterization of cases with a pre-operative treatment as well as to compare the treatment of screen-detected cases with ICs, under the hypothesis that the latter is at a more advanced stage.

SURVIVAL

It is of interest to compare the survival of screen-detected cases with that of ICs. The survival of screen-detected cases is affected by the lead-time bias, i.e., an artificial increase in survival due to diagnostic anticipation. This bias can be corrected by using a common starting point, such as the date of the screening test, for screen-detected cases and ICs.

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Recommendations

Screening programmes should regularly monitor:

- the proportional incidence of ICs as well as test and programme sensitivity, providing information about the definition of the expected CRCs (underlying incidence) and of the observed ICs. The ICs identification can be done using HDRs and following the methodology proposed in this Manual;
- the comparison of the distribution by stage at diagnosis of ICs, screen-detected carcinomas, and cases occurring in the non-responders.

Clinical documentation of the ICs diagnosed after a negative TC should be acquired.

The screening programme endoscopists should take part in periodic multidisciplinary meetings on the revision and classification of these ICs. Furthermore, programmes should provide a systematic audit to highlight critical aspects. These activities should be an essential part of a screening programme's periodic monitoring

The collection of ICs and the calculation of related indicators are complex and can be performed every two or three years. Instead, the revision of ICs occurring after a negative endoscopy do not necessarily need to be performed on the totality of ICs and should be carried out yearly.

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