

Evolution of colorectal cancer epidemiology in a setting of opportunistic screening. A 20 year national survey in Luxembourg.

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Abstract

Invasive colorectal cancer (CRC) is the second leading cause of cancer death in Luxembourg. There is no organized screening programme in Luxembourg. This study aims to obtain a precise epidemiological description of the evolution of invasive CRC and high grade intraepithelial neoplasia (HGIEN) from 1990 to 2009, extracted from the database of the Morphologic Tumour Registry. Tumor stages and observed survival rates were also recorded. They were compared to the change in use of colonoscopic procedures. During the 20-year period, 4810 invasive CRC cases and 1180 HGIEN were recorded. Incidence rose from 1990 to 2005 and declined thereafter, especially in women. A sharp rise in HGIEN was noted from 2004 onwards, paralleling the rates of colonoscopies. 76 % of CRC cases were found in advanced stages pT3 and pT4. The pT stage distribution did not change over the observation period. Observed survival rates improved during the study period. Conclusion: Under opportunistic screening conditions, mainly through colonoscopy, the incidence of CRC was declining in recent years, whereas HGIEN incidence is rising in Luxembourg. Tumor pT staging remained unchanged whereas survival rates improved. We conclude that opportunistic screening is of little benefit for CRC prevention. A national organized screening programme is warranted. (*Acta gastroenterol. belg.*, 2013, 76, 25-33).

Key words : colorectal cancer, epidemiology, incidence, screening, colonoscopy.

Background

Colorectal cancer represents a significant public health care burden in Western countries (1,2). Approximately 435,000 new patients are diagnosed every year, and CRC causes more than 200,000 deaths per year in Europe (3). For these reasons “organized” CRC screening and prevention programmes are recommended (4-9). CRC screening has been shown to be cost-effective, irrespective of the method used (10,11). Moreover encouraging survival data have recently been documented in the USA (12,13) as well as in a German screening cohort based on high quality colonoscopy (14,15). On the other hand, opportunistic screening has not been shown to represent a valid strategy to reduce cancer incidence nor mortality, e.g. in breast cancer (16). Because the use of colonoscopy along with the removal of adenomas may have the potential to reduce CRC cancer mortality (17), it tends to become the method of choice for CRC screening and prevention – at least in high risk subgroups (2,18).

In Luxembourg no organized CRC prevention programme exists so far ; screening mainly relies on voluntary, so-called “opportunistic”, diagnostic examinations.

We have conducted this survey in order to eventually promote CRC screening efforts in Luxembourg by collecting the epidemiological data baseline from the last 20 years.

Methods

This is a retrospective analysis of the databases of the Morphologic Tumour Registry (MTR) and the Central Department of Pathology (National Health Laboratory - LNS) in Luxembourg. It concerns the period from 1990 to 2009 (19). These databases contain all incident cases of CRC and adenomas, since all histological specimens originating from diagnostic or therapeutic procedures (endoscopies as well as surgical interventions) performed on persons residing in the Grand-Duchy of Luxembourg are automatically recorded from 1990 on. Following the 2010 WHO-classification, the term “high grade intraepithelial neoplasia” (HGIEN) was used synonymously for “adenoma with severe atypias”, “adenoma with severe dysplasia” or “high grade adenomas” (20). All HGIEN and invasive colorectal adenocarcinomas removed by surgery were classified following the histological WHO-criteria and the TNM-system of the “International Union Against Cancer” (21-23). Residents treated outside of Luxembourg as well as non-residents treated in Luxembourg are not included in this survey. All incident cases of adenocarcinomas of the colon and rectum, as well as all cases of adenomas histologically characterized as high grade intraepithelial neoplasia, were individually reviewed. This survey does not focus on cases of so-called “advanced adenomas” characterized by a villous or tubulo-villous histology, or greater than 10 mm (24). Malignant neuroendocrine carcinomas, malignant lymphomas as well as multifocal carcinomas were excluded.

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Cases were stratified by sex, age and calendar year (date of diagnosis) from 1990 until 2009.

These data were used to calculate raw and age-standardized incidence rates and were compared to epidemiological data from selected international regions (25).

The number of all colonoscopic examinations (total as well as partial examinations) performed in Luxembourg from 1990 to 2009 were provided by the National Health Insurance Service (Caisse Nationale de Santé - CNS) (26).

Tumour stages (pT) were reviewed, according to the TNM classification and stratified by calendar year (22). Cancer stages (I-IV) could not be correctly determined because the databases did not have information on the presence of distant metastases in all patients.

The mortality data were issued from the National Death Registry and the Annual Reports of Demography published by STATEC (Central Service of the Statistics and the Economic Studies of the State) (27,28). The "observed" survival rates were analysed in relation to the pT stages. Tumour-specific survival rates were impossible to calculate, because of the anonymous nature of death cause certificates in Luxembourg.

Statistical analyses on CRC incidence rates (crude and age-specific) were calculated by the direct method, the standard error of the age-standardized rates by the Poisson approximation (29). 5-year observed survival rates were calculated from the date of diagnosis and following the Kaplan-Meier method (29).

The study respected all criteria for confidentiality and all legal aspects in the Grand-Duchy of Luxembourg.

Results

Tumour incidence

From 1990 to 2009, 4810 cases of invasive CRC and 1,180 cases of HGIEN were recorded (Fig. 1).

Figure 2 shows the age-standardized (world standard population) incidence rates of invasive CRC and HGIEN per 100,000 persons in males and females from 1990 to 2009 by year of diagnosis. The rates in males are about twice as high than in females for both invasive CRC and HGIEN. Invasive CRC incidence rates seem to decline steadily from 2005. Case numbers of HGIEN showed a steady increase from the early 1990s, but especially in the years from 2004 onward, when they nearly doubled within 5 years. HGIEN incidence rates markedly increased during the observation period.

The distribution of invasive CRC according to the age at diagnosis has been examined by age-specific incidence rates (Fig. 3). Male and female rates are both low until the age group of 45-49 years. Rates rapidly increase thereafter from about 18 per 100,000 in men (45-49 years at diagnosis) to 451 per 100,000 for males of 80 years & older. Female incidence rates are lower but the evolution parallels that of males.

Figure 4 shows colo-rectal cancer age-standardized (world population) rates in Luxembourg as compared to selected international regions. In general the rates in limitrophic regions of Germany, France and The Netherlands seem to be higher than in Luxembourg, while Finland, Sweden and Belgium have lower rates.

Diagnostic procedures

Figure 5 shows the evolution of colonoscopic procedures as compared to the total CRC incidence evolution. Data on crude incidence rates were here considered. Colonoscopies more than doubled during the study period reaching 14,443 procedures per year in 2008.

Tumour (pT) stages

Tumour pT stages were aggregated in 5-year periods from 1990 to 2009 (Fig. 6). Overall, 76% of all CRC cases were found in stages pT3 and pT4. Although there was a slight increase in pT1 and pT2 stages in the last 5-year period, there was no significant variation concerning the advanced tumour stages throughout the whole study period.

Even in the most recent time period from 2005 to 2009, 821 cases detected were in stage pT3 and pT4 while only 301 were detected in earlier stages (Fig. 6).

Survival rates

Because of methodological problems with death certificates in Luxembourg we were unable to calculate tumour-specific death rates. However, 5-year observed survival probabilities (%) from date of diagnosis are shown in Figure 7. It can be seen that 5-year survival rates in males and females increased from about 40% in the 1990-1994 group to over 65% in the 2000-2004 group.

Figure 8 documents the importance of detecting the tumours at an early stage, using 5-year overall survival rates (all death causes included) following pT tumour staging. Patients with tumours detected at stage pT4 have less than 25% five-year survival expectancy compared to about 45% for those detected at stage pT3 and 75% for pT1 and pT2 stage patients.

Discussion

Colorectal cancer (CRC) is one of the most common types of cancer in Luxembourg (19). It represents the second cause of cancer death, after broncho-pulmonary cancer (27). Because all cancer cases are recorded in the Morphologic Tumour Registry (MTR) since 1990, this survey may serve as a valuable overview of CRC evolution in a well-defined Western European region of about 500,000 inhabitants. CRC epidemiology in Luxembourg has only partially been reported (30,31). Tumour incidence in Luxembourg is comparable to that of other European regions or countries with similar socio-economic development (Fig. 4). It is important to note that invasive

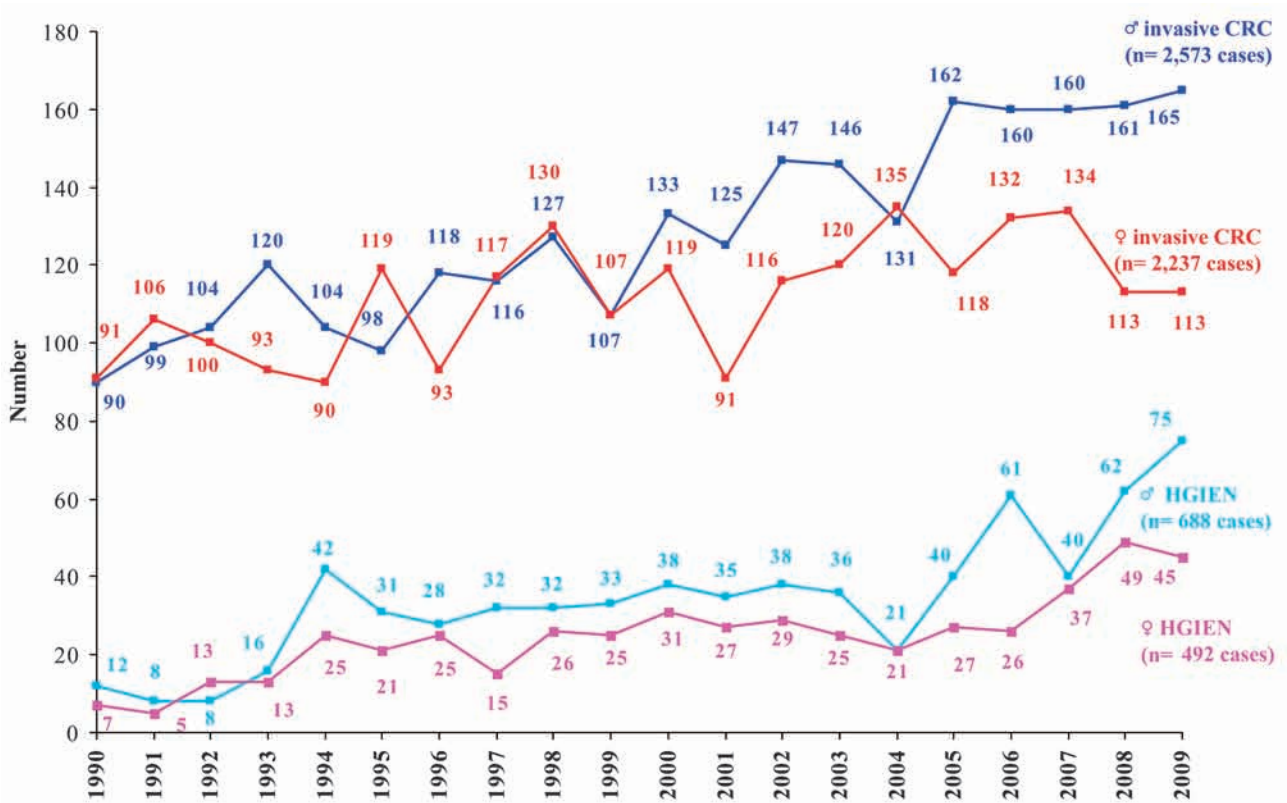


Fig. 1. — Absolute numbers of invasive colo-rectal cancers (n = 4,810 cases) and colo-rectal high grade intraepithelial neoplasias (n = 1,180 cases) ; males, females ; 1990-2009 ; Luxembourg.

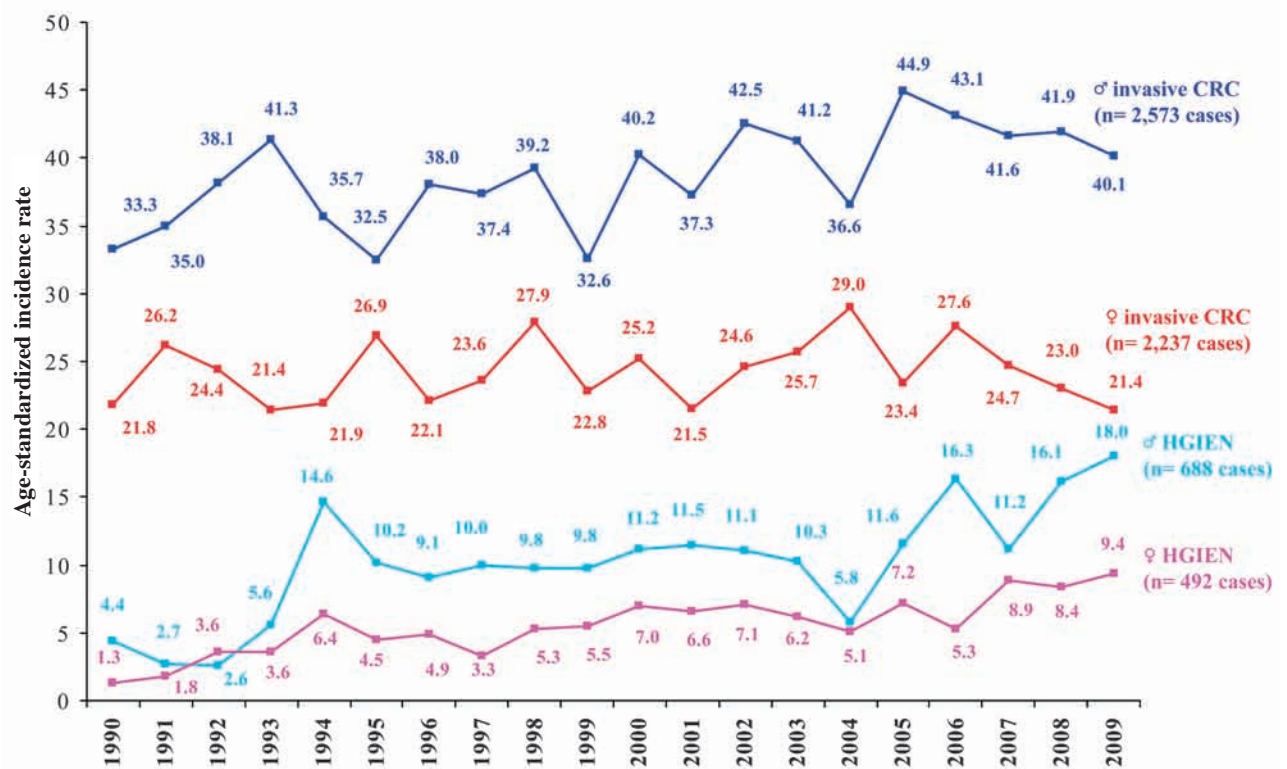


Fig. 2. — Age-standardized (world standard population) incidence rates of invasive colo-rectal cancers (n = 4,810 cases) and HGIE (n = 1,180 cases) ; males, females ; 1990-2009 ; Luxembourg.

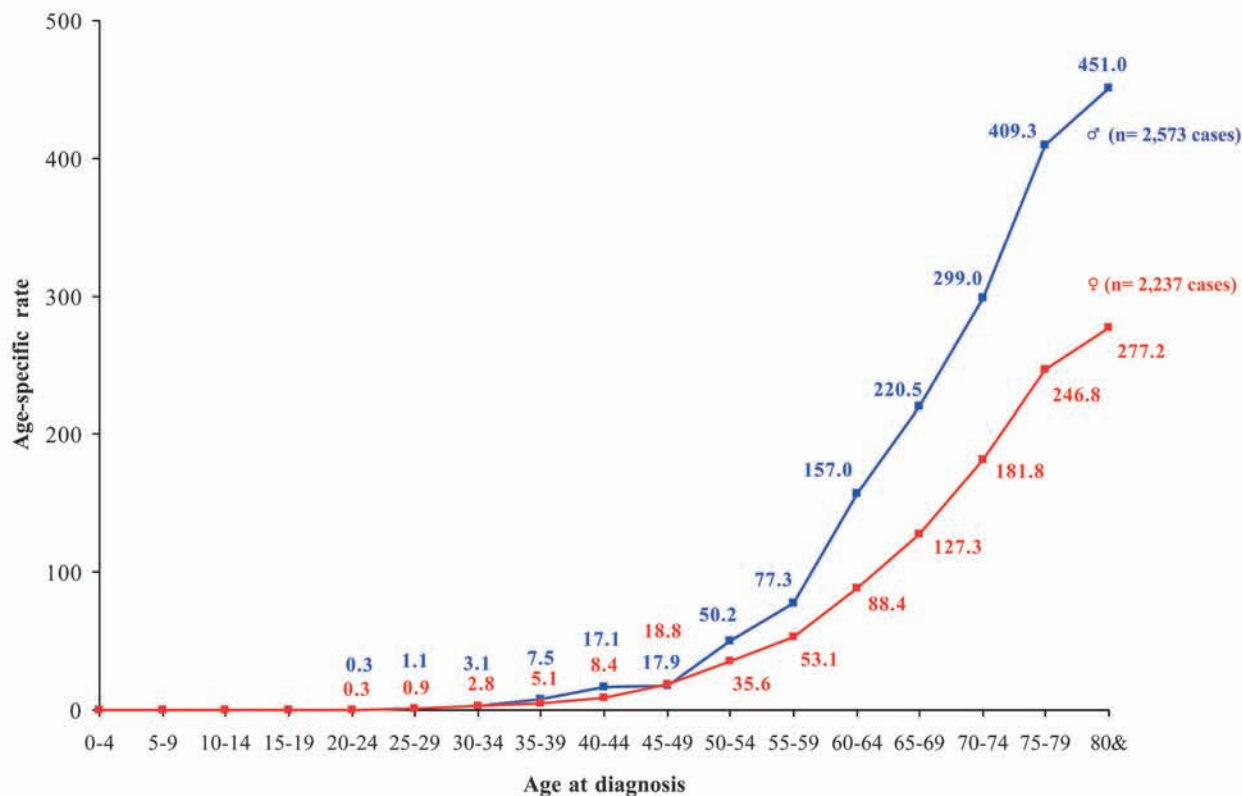


Fig. 3. — Age-specific incidence rates of invasive colo-rectal cancers (n = 4,810 cases) by age groups ; males, females ; 1990-2009 ; Luxembourg.

CRC incidence only very recently started to decline in Luxembourg (Fig. 2), whereas this phenomenon has been described earlier in other Western countries (3). Not surprisingly, the apparent fall in CRC incidence is accompanied by a marked increase in HGIEN cases (Fig. 2). This might be due to more widespread use of colonoscopy as a screening tool as well as a better colonoscopic technique. The considerable rise in the high risk precursor lesion (HGIEN) incidence from 1994 on may be interpreted as an encouraging result. There is no doubt that HGIEN removal prevents CRC development (13-15,17).

An officially “organised” CRC screening and prevention campaign has never taken place in Luxembourg. Therefore this study can also serve as an example of CRC epidemiology in a so-called “opportunistic” screening setting. Screening awareness efforts in Luxembourg mainly rely upon private initiatives and clearly favour total colonoscopy as the most reliable screening tool, following North American guidelines (6-8), whereas faecal

occult blood test (FOBT) has been favoured by public health care providers prior to the year 2000. Consequently, most screening examinations are probably due to self-referral of patients for colonoscopy. This is reflected by the evolution of the use of colonoscopy (Fig. 5). Nevertheless the apparent parallel between CRC and HGIEN cases and colonoscopic procedures cannot be interpreted as a cause-effect relation. Indeed the population of Luxembourg increased by approximately 30% (1990 = M : 188,344 + F : 196,056) and (2009 = M : 249,406 + F : 252,660) over the study period (28). A rise in life expectancy might also explain the rise in CRC incidence until the years 2004/2005 (Figs. 2), as is corroborated by the advanced age at diagnosis (Fig. 3).

Both CRC incidence and mortality have been decreasing worldwide in recent years (2). This holds particularly true for countries where CRC screening is actively recommended, such as in the USA (6-8) or Germany (32). The reasons for this positive evolution have been

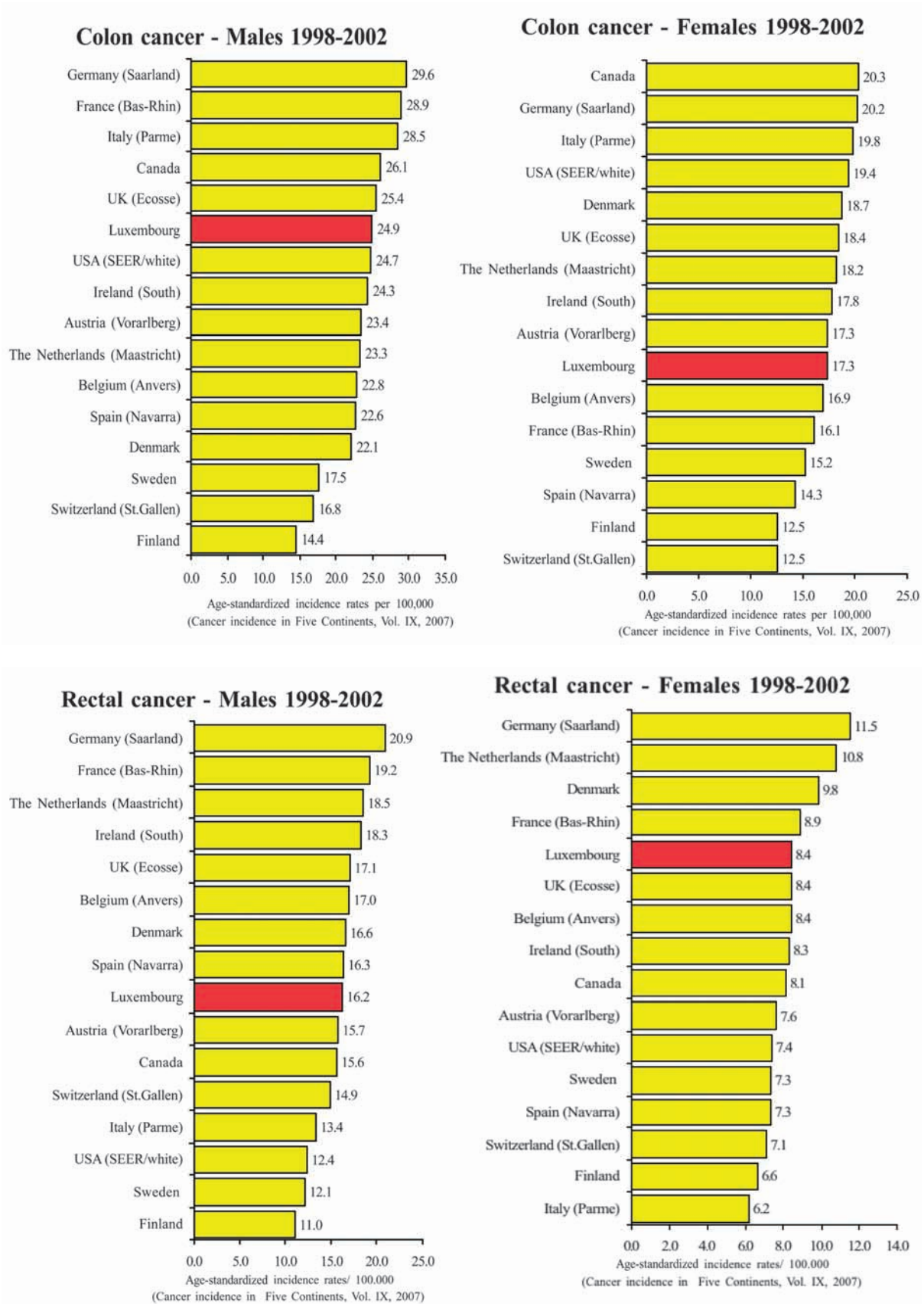


Fig. 4. — Age-standardized (world standard population) incidence rates of invasive colo-rectal cancers (Cancer Incidence in Five Continents, Vol. IX, 2007) n = 4810 cases ; males, females ; 1998-2002 ; Luxembourg.

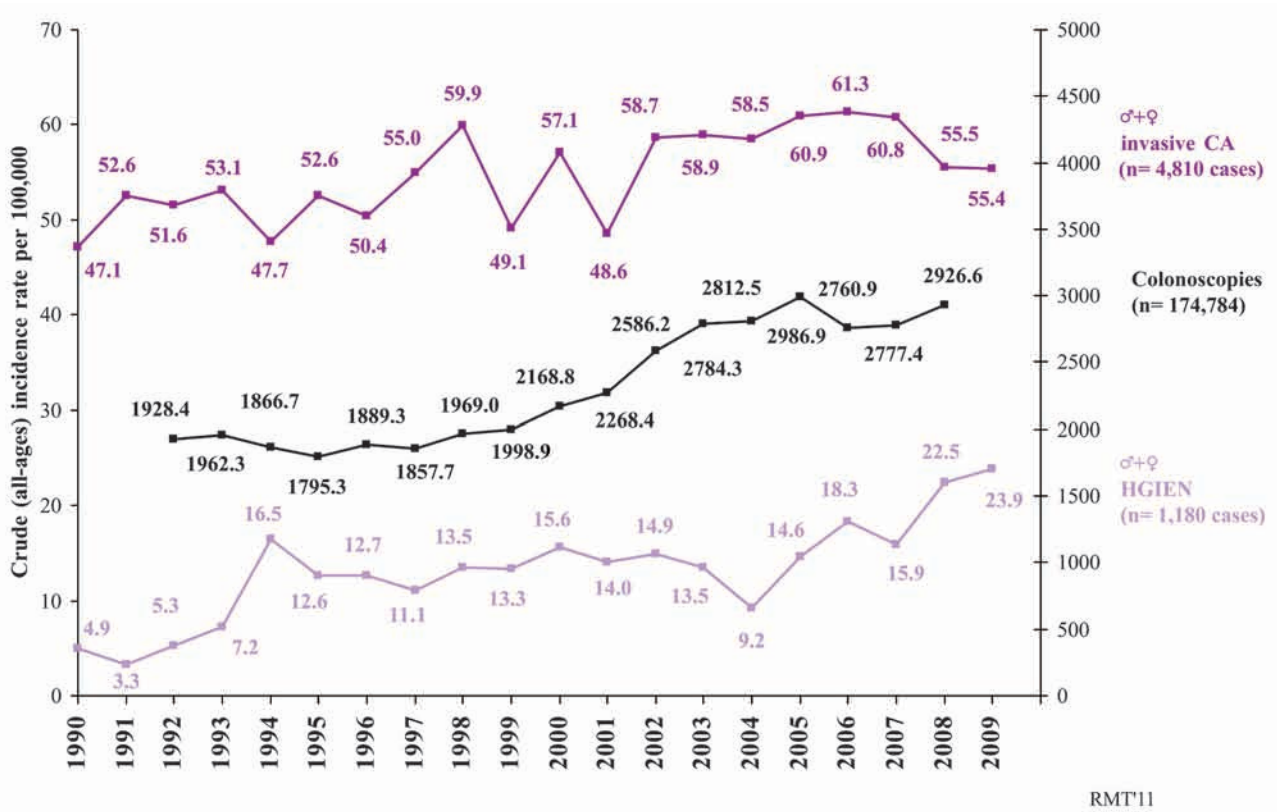


Fig. 5. — Crude (all-ages) incidence rates per 100,000 of invasive colo-rectal cancers (n = 4,810 cases), HGIEN (n = 1,180 cases) and colonoscopies (n = 174,784 individuals) ; males, females ; 1990-2009 ; Luxembourg.

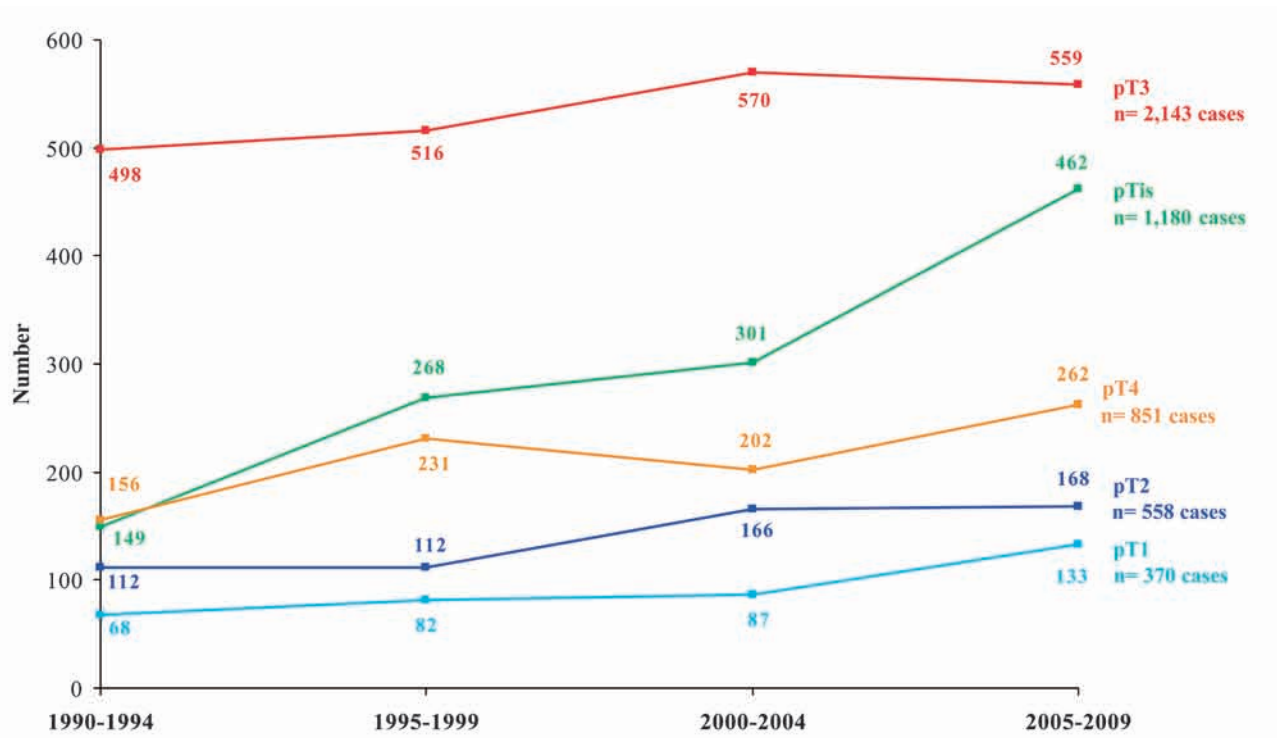


Fig. 6. — Effective numbers of invasive colo-rectal cancers (n = 3,922 cases) and HGIEN (n = 1,180 cases) by size (pT/UICC) ; males and females ; 1990-2009 ; Luxembourg.

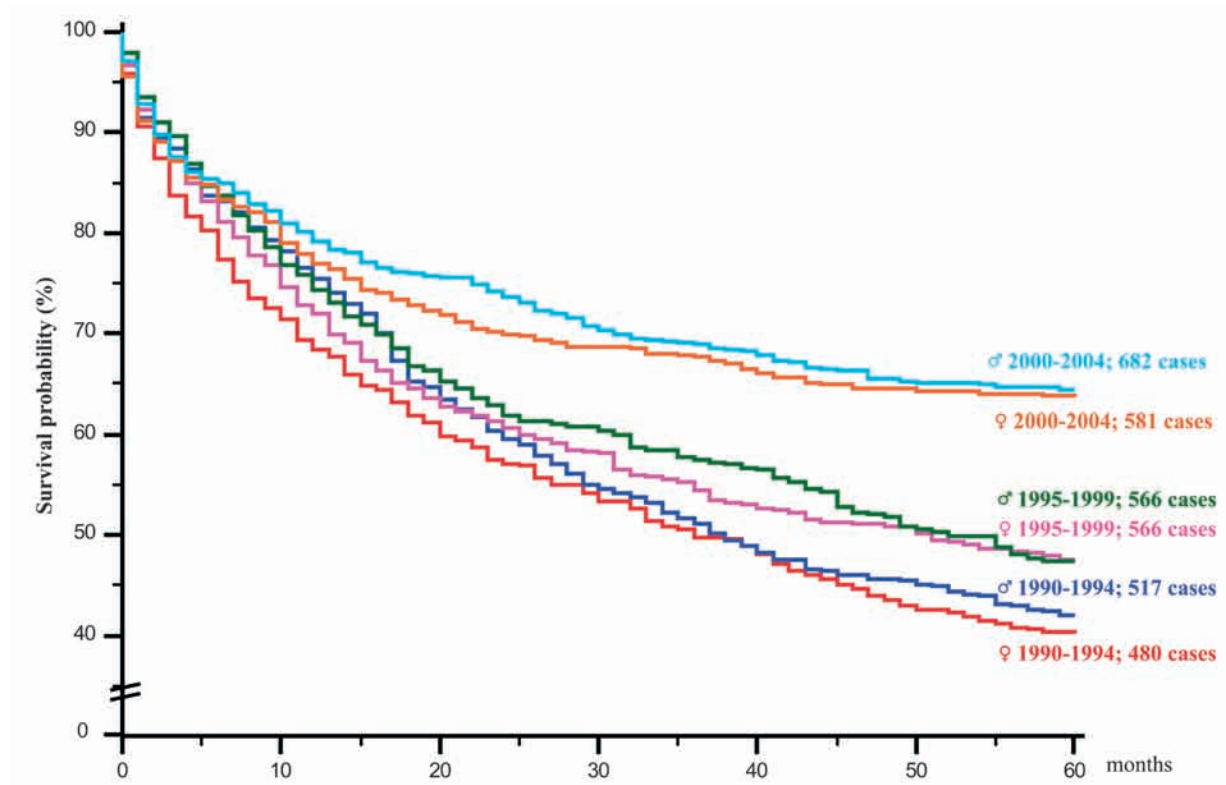


Fig. 7. — Five-year “observed” survival probabilities (Kaplan-Meier method) for invasive colo-rectal cancer, (n = 3,392 cases) by 5-year periods, males and females ; 1990-2004 ; Luxembourg.

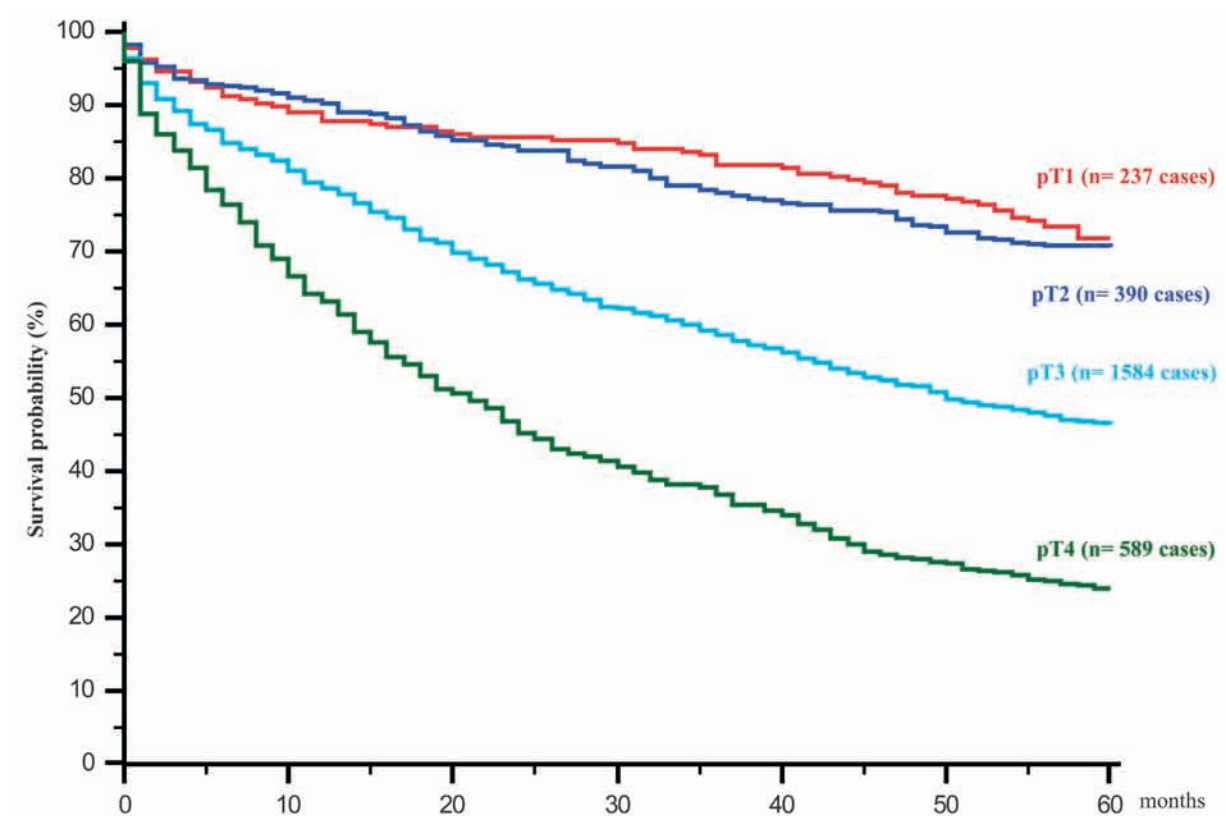


Fig. 8. — Five-year “observed” survival probabilities (Kaplan-Meier method) for invasive colo-rectal cancer, (n = 2,800 cases) by degree of infiltration [pT(UICC/2002)] ; males and females ; 1990-2004 ; Luxembourg.

attributed to detection at a more favourable tumour stage as well as the removal of polyps (i.e. adenomas) (6-8). Pure screening methods such as FOBT have been shown to detect tumours at an earlier stage followed by better survival chances of about 15 % (33). Truly preventive measures aimed at the removal of precursor lesions, i.e. colonoscopy with polypectomy, will presumably have an effect on incidence reduction (13-15,17,34). One randomised controlled trial showed that flexible sigmoidoscopy screening reduced CRC incidence and mortality (35). It is important to note that currently, there is a lack of conclusive prospective studies with total colonoscopy concerning this last point (5), although such studies are under way. Indirect evidence of efficacy comes from the large prospective observational US National Polyp Study Group comparing CRC incidence in a population that underwent colonoscopy with polypectomy with the incidence in historical reference populations (13). Our study clearly shows that purely opportunistic screening, although performed within a context of unrestricted availability of modern colonoscopic facilities, failed as a preventive method. Not only did CRC incidence rise until very recently, but very strikingly tumour pT stages remained unaffected even during the last few years of our survey (Fig. 6). This may be due to the fact that a significant proportion of persons at risk were not sufficiently aware of screening efforts (under-use). In the absence of adequate and necessary quality evaluation of colonoscopies (36), we are not able to speculate about potential over-use of colonoscopic resources by wrong target populations (37). Opportunistic screening has been shown to be less efficient and more costly both in terms of resources and adverse outcomes and thus could not be recommended as an alternative to organized screening (38). Therefore we strongly believe that public information campaigns are necessary, the organisation of a formal screening programme remaining a political and financial issue. Whether such a programme is cost-effective remains an open question influenced by local factors, but has been answered positively in USA (10,11) and in Europe (5).

The prognostic improvement of CRC patients in Luxembourg is most probably due to progress in tumour therapy, since tumour pT staging remained almost unchanged over more than 20 years. This result corresponds to the figures recently reported in other Western countries such as the Netherlands (39), but with the notable difference of early tumour detection explained by effective screening efforts.

Hence we believe that there is a great deal of improvement possible in CRC screening and prevention in Luxembourg, via an organized programme of high quality colonoscopies.

Conclusions

This national observational study may serve as a reference for epidemiological evolution of CRC in a setting

without organised screening. Falling CRC incidence rates observed recently may be attributed to the increased use of opportunistic colonoscopy with polypectomy, but is counterbalanced by the absence of improvement in tumour staging. Furthermore cost-effectiveness remains highly questionable in this setting. This study confirms the decline of CRC mortality. Efforts towards an official nationally organised CRC screening and prevention campaign seem desirable in Luxembourg.

Competing interests

The authors declare that they have no financial and non-financial competing interests.

Authors' contributions

All authors (PP, RS, KA, MB, CC) collaborated intensely on all aspects of the manuscript, from research design to data preparation and presentation. PP, RS and KA wrote and all authors approved the final manuscript.

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