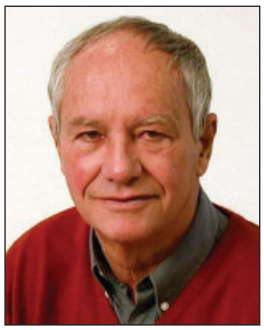
Melvin Schapiro, M.D., Series Editor

Influence of Screening on the Incidence and Mortality of CRC



Rene Lambert

Colorectal cancer accounts to just less than 10% of the global cancer burden in the World; this justifies prevention through screening and early detection. In men and women the risk of having a colorectal cancer increases from the age of 50 years. Randomized trials on the benefit of screening with the fecal occult blood test show a small impact on the specific mortality, no impact on global mortality, neither on the incidence of colorectal cancer. An established policy of screening for colorectal cancer in a country is based on organized protocols with the fecal occult blood test and opportunistic screening with endoscopy. Endoscopic screening aims to early detection of cancer and reduction of the incidence through removal of precursor polyps. The efficacy of the preventive strategy is confirmed in the Surveillance, Epidemiology, and End Results (SEER) registries and vital statistics of the USA by a decline in the curves of incidence and mortality obtained from cancer registries and from vital statistics of this country.

INTRODUCTION

The Burden of Colorectal Cancer

The burden of colorectal cancer was estimated in the IARC database Globocan 2002 (1) at 9.4% of the global cancer burden in the World. This represents 550,000 incident new cases and 278,000 deaths for men and 743,000 incident new cases and 255,000 deaths for women. Of course the annual numbers of incident new cases of cancer and of deaths from cancer do not correspond to the same persons. Colorectal cancer is most frequent in North America, Australia, New Zealand and parts of Europe. For 2002 the numbers of incident new cases was estimated (1) at 184,000 in North America, 46,000 in South America 7,500 in Central America, 24,000 in Africa, 360,000 in Europe with Russia, 369,600 in Asia. In the aging population of the world a further increase of the numbers is expected in the next decades; this applies particularly to emerging countries of the World, in Asia from changes in lifestyle and in environmental socio-economic factors in addition to the aging factor.

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In cancer registries (2) and in the vital statistics of a country, the burden of colorectal cancer is summarized as a rate for 100,000 persons. *The crude rates of incidence or mortality per 100,000 persons*, for men, for women or for both sexes correspond to the actual burden in the country. The risk of having a colorectal cancer under the age of 50 years is very small and then increases in successive age groups from 10 and 10 years: the *Age Specific Rate of incidence or mortality for 100,000 persons* is also a crude rate. In the white population of the USA, (SEER, 17 registries (3), for the period 2000–2003 the respective values of the Age Specific Rate of incidence per 100,000 were 13.4 (40–44 years-old), 49.8 (50–54 years-old) 122.1 (60–64 years-old) and 250.7 (70–74 years-old) . When comparing the risk of cancer in two populations or in two periods for the same population (time trends), the differences in the pyramid of ages introduce a bias which is controlled when using a *Age Standardized rate (ASR) of incidence or mortality for 100,000* which is adjusted to a standard of population. A World population standard is used for comparisons between countries; a National population standard is used to follow time trends in the same country (for example the US population in 2000 for time trends during 1975–2003 in the SEER Registries). The adjusted ASR is required to estimate variations of the incidence and mortality in relation to environmental factors or to an intended policy screening.

Another parameter is the *survival rate from cancer* which is obtained in Cancer registries which have a follow-up of the cases. The five-year survival rate represents the prognosis of the tumor after detection and is a crude rate, often adjusted to remove all causes of death except the cancer analysed (*five-years relative survival rate*). The survival rate varies with the stage of the tumor at detection. The evolution of the survival rate is influenced by the progress in early detection, but also the progress in treatment (Table 1).

Table 1.
Evolution of the five years relative survival rate from colorectal cancer during the period 1975–2002 in the USA.

During this period the progression of survival (+30% in men and +26% in women) results mostly from improved treatment. During the same period the increase in the proportion of cases detected at the localized stage was less: +18% (both sexes). Source: SEER 9 registries in the USA.

	Men	*Women*
1975–1979	50.2%	52.3%
1985–1989	60.5%	59.8%
1995–2002	65.4%	66.3%

EARLY STAGES OF NEOPLASTIC COLORECTAL LESIONS

Neoplastic lesions of the colon include confirmed carcinoma and premalignant precursors. Autopsy and colonoscopy studies confirm a fairly high prevalence (in the range of 30%) of adenomatous polyps in the adult populations of various countries. This means that the majority of precursors will never progress to cancer. Neoplastic lesions are assumed to be completely curable when invasion in the wall of the colon and rectum is limited to the mucosa or submucosa. If the endoscopic appearance of a lesion suggests that extension is superficial in depth, it is classified (in opposition to types 1 to 5 for advanced cancer) as type 0. Protruding or polypoid adenomatous lesions (type 0-I), pedunculated or sessile, are conspicuous and easily detected at endoscopy. Nonprotruding or nonpolypoid lesions, less conspicuous, can be misdiagnosed; they are slightly elevated (0-IIa), slightly depressed (0-IIb), or completely flat (0-IIb) (4). Most nonpolypoid lesions are slightly elevated and show a very low potential for malignancy, while the less frequent nonpolypoid depressed lesions, even when small, often show focal cancer. Japanese authors consider that Flat (nonpolypoid) adenomas, can be precursors of large nonpolypoid lesions, or alternatively polypoid lesions. Small depressed adenomas may represent the earliest macroscopic stage of adenoma growth with progression from depressed through flat and then polypoid. Serrated adenomas, often misdiagnosed for hyperplastic nonneoplastic lesions, show areas with low-grade or high-grade intraepithelial neoplasia, and play a role of precursor.

For the pathologist superfical neoplastic lesions are described in the categories of the Vienna classification—low-grade non-invasive intraepithelial neoplasia—high-grade non-invasive intraepithelial neoplasia-invasive high-grade intraepithelial neoplasia (intramucosal carcinoma)—submucosal carcinoma. The terms adenoma or dysplasia correspond to low-grade or high-grade intraepithelial neoplasia in the Vienna classification

Superficial neoplastic lesions are the target of screening. The design of cancer prevention programs still relies mostly on the adenomatous polyp-cancer sequence; in the USA clinical experts and pathologists often use the terminology *"advanced adenoma"* to describe polyps at least 1 cm in diameter, or with a villous architecture, high-grade intraepithelial neoplasia or with focal cancer. On the other hand, the flat adenoma-cancer sequence, described in Japan, and confirmed in Western countries (5-8), is now considered to be responsible for up to 40 % of advanced cancer . This new concept has an impact on the efficacy of filter and diagnosis tests and must be taken in consideration in screening protocols .

DEFINITION OF SCREENING

Secondary prevention is based on early diagnosis of cancer at a curable stage in asymptomatic persons (9), and also diagnosis of the precursors (benign neoplastic lesions). Mass (or organized) screening organized by the National Health Authorities is proposed to a defined target population and monitored by guidelines. Mass screening protocols are based on a simple filter test followed by a detection test in persons having a positive response. The efficacy of a mass screening policy depends on the covering of the selected target and compliance to the procedure. Individual (or opportunistic) screening is the detection of a unrecognized disease in apparently well persons at the initiative of the person, or the responsible physician. The target is persons conscious of their health rather than those with a risk higher than average. There are no strict guidelines and the evaluation of results is often incomplete. Organized and individual screening are complementary because they apply to slightly different targets, increasing therefore the coverage of the population.

EVALUATION OF SCREENING

Organized screening programs require an evaluation of benefit and cost (9). The benefit for a person screened as "negative" is reassurance. The benefit for a person screened as "positive" is treatment of the tumor at a curable stage and can be evaluated in life-years (LY) gained. A cost-effective (C/E) intervention produces additional benefits that are worth the additional cost, compared to a "no" screening strategy (10). Organized screening also requires an evaluation of drawbacks. Some persons who do not have the disease, and yet test "false positive," are affected by adverse consequences which include the anxiety associated with testing "positive" and the morbidity associated with the unnecessary procedures. Persons screened as "true positive" may also be affected by the morbidity associated to diagnostic procedures and to treatment. Furthermore there is a risk of over-treatment: not all neoplastic lesions (including early cancer) detected and treated in those persons would have had an impact of life span. In assessing the efficacy of an intervention aimed at prevention of cancer, the specific mortality from that tumor is the most important indicator; if there is no decrease the impact on prevention is very small. Time trends on mortality are studied as ASR rates per 100,000. Incidence is the other parameter which should also be adjusted as ASR incidence .

At first, the efficacy of the intervention is assessed on trials conducted in limited numbers of persons. Retrospective case-control studies explore the occurrence of a procedure of early detection, in the antecedents of cases (cancer) and of controls (no cancer). Prospective cohort, or observational studies, analyze the occurence of incident cancer during the follow-up of persons which were submitted to a procedure of early detection. Both types of studies are exposed to uncontrolled bias, concerning the selection of the persons and environmental factors, while randomized trials allow to control all bias. The methods of Evidence Based medicine have been applied to the evaluation of screening in the Cochrane Reviews (11–13). A priority is then attributed to randomized trials. The long term impact of organized and individual screening on incidence, mortality and survival from cancer after the introduc-

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tion of the intervention, is explored in the Vital Statistics of the country and in Cancer Registries.

The critical interpretation of the data produced by trials, vital statistics and cancer registries, takes in account time trends bias during the period following the introduction of the intervention. There are three major bias in interpretation of mortality data:

1. The improved survival and mortality in the screened persons may result from the preferential detection of better cases having a slow progression (*selection bias*), while severe cases are under-detected by the intervention.
2. Technical progress in methods of early detection and treatment increases the proportion of stage I and II tumors with a better prognosis (*stage migration bias*) in both screened and unscreened persons.
3. The interval between detection and death from cancer is by definition longer in persons detected at a preclinical stage, than in those detected at a symptomatic stage; this does not prove that there has been a gain in life span (*lead time bias*). Incidence data are also subject to bias : a decreased incidence may result from a spontaneous variation rather than from the intervention, as shown for stomach cancer in Japan. An increased incidence may result from a spontaneous variation or from over-diagnosis.

STRATEGIES OF SCREENING FOR COLORECTAL CANCER

Colonoscopy is still the gold standard procedure for the early detection of colorectal cancer and its adenomatous precursors (9). Detection can be coupled to endoscopic treatment of the benign precursors. This gold standard status does not means that colonoscopy is the more adapted procedure in a mass screening strategy; limiting factors include a limited compliance, high cost and a small toll of severe complications (14,15). On the other hand colonoscopy should be the elective primary procedure in individual screening. The yield of screening colonoscopy in a group of average risk persons, aged 50 years or more, is less than 1% for cancer, less than 10% for advanced adenomas, and in the range of 25% to 30% when all adenomas are considered. There is indirect evidence from non-randomized trials that colonoscopy and polypectomy, may reduce cancer mortality. A case-control study has estimated the reduction in mortality afforded by endoscopic procedures and polypectomy at 59% (16). There is also an impact on the incidence of colorectal cancer following endoscopic treatment in persons having adenomatous polyps; in the prospective analysis of the National Polyp study (17) in the USA the reduction of the risk was estimated at 75% using a comparison with an unscreened population. The chance of finding a cancer during the next five years after a negative colonoscopy is very small. This justifies the tendency to propose screening colonoscopy from age 50 years at 10 year intervals or once in a life and to establish guidelines for endoscopic screening and surveillance (18–21).

Rigid rectosigmoidoscopy is now abandoned in screening protocols, while *flexible sigmoidoscopy*, which explores the distal colon and the rectum, is often proposed in screening strategies because of a better acceptance than colonoscopy (22). A major advantage of the procedure is that it can also be performed by trained specialized nurses at a lesser cost. A disadvantage is the heterogeneity of the results obtained by distinct operators. The efficacy of rigid or flexible sigmoidoscopy has been evaluated in case-control or observational studies (23–26). The Kaiser Permanente Health Maintenance Organization, compared the exposure to rigid sigmoidoscopy screening during the previous 10 years in cases (distal CR cancer) and in age and sex-matched controls (no cancer): sigmoidoscopy reduced by 59% the incidence of distal colorectal cancer, and the reduction for colorectal cancer in all sites was estimated at 30% (24). In Scandinavia the NORCCAP trial has shown a higher yield of detection with flexible sigmoidoscopy than with the FOBT (25). In the USA, a cohort study conducted in 24,744 health professionals has shown that screening flexible sigmoidoscopy reduces mortality from colorectal cancer by 50%, and incidence by 44% (26). Randomized screening trials of flexible sigmoidoscopy are in progress: the PLCO (prostate, lung, colorectal and ovarian cancer) screening trial in the USA is examining the efficacy of this procedure repeated at five year intervals (27), while trials in the UK and in Italy (28) are evaluating a single flexible sigmoidoscopy offered at age 55–64 years. In screening protocols based on flexible sigmoidoscopy, colonoscopy is still required if

Table 2.
Randomized trials on colorectal cancer with the guaiac fecal occult blood test: the protocol

	Target	*Campaigns*	*Test*	*Length FU*
Minnesota Trial (31-33)	volunteers cancer 1 league	annual test	rehydrated test	18 years
Nottingham Trial (34, 35)	population based	biennial test	non-rehydrated test	11.7 years
Funen Trial (36, 37)	population based	biennial test	non-rehydrated test	17 years
Burgondy Trial (38)	population based	biennial test	non-rehydrated test	11 years

there is a positive finding. For persons with negative findings the guidelines recommend that flexible sigmoidoscopy be repeated five years after the initial negative procedure.

Fecal Occult Blood Test (FOBT), either with the guaiac method or the immunochemical method (29), is currently accepted as a filter test in organized screening protocols. Colonoscopy is then proposed to persons with a positive test. With FOBT there is a significant proportion of false positives, the sensitivity is not over 50% for cancer, less than 20% for precursor polyps, and still lower for depressed lesions. Screening with the FOBT is proposed to persons at risk for sporadic colorectal cancer, i.e. men and women from the age of 50 years, and repeated in successive campaigns. There is no benefit in prolonging screening above the age of 70 years for persons who entered at age 50 years in the protocol and always tested "negative." FOBT is still the most used filter test, but is far from being a good test (30) and could be replaced in the future by Fecal DNA Tests. In spite of its limits in sensitivity and specificity, a robust evidence (Tables 2 and 3), is collected in randomized trials, on the capacity of this test (repeated at annual or biennial intervals) to reduce mortality from colorectal cancer. The fairly good results obtained in the Minnesota trial (31–33), after a 18-year follow-up (33% reduction in mortality, 20% reduction in incidence) are explained by the annual repetition of a rehydrated test with a 4-fold increase in "false positive" and the high compliance of persons selected as volunteers rather than being population-sorted. The impact on incidence in this trial is a consequence of the high proportion of screenees submitted to colonoscopy (38%). Results were not as good when the randomized trials were conducted with a methodology compatible with a mass screening intervention; i.e. in population-sorted persons and a biennial repetition of a non-rehydrated FOBT, giving less "false positive." In the three European trials conducted in Nottingham (34,35), Funen (36,37), Burgondy (38), the proportion of screenees submitted to colonoscopy is small (not over 5%) and there is no impact on incidence; the impact on mortality in the group submitted to screening is not over 15%, being as low as 11% when the follow-up is prolonged 18 years in the Funen trial (37).

IMPACT OF SCREENING ON MORTALITY AND INCIDENCE FROM CRC

Impact on Mortality from Colorectal Cancer

The impact of screening with FOBT on mortality from colorectal cancer is small but accepted in Evidence Based Medicine and confirmed by the decreasing time trend occurring in countries having an established policy of organized screening and opportunistic screening with colonoscopy. In the USA, for the period 1975–2003, the SEER Registries (3) show a 32.5% decrease of the ASR mortality rate. The origin of the variation is multifactorial: general improvement in therapeutic procedures, reduction of incident cases after endoscopic resection of precursors, detection of cancer at an earlier stage with an increased proportion of localized tumors (+18%). In Japan, the risk of colorectal cancer is increasing in the statistics since 1975; the mortality from colorectal cancer was increasing during

Table 3.
Randomized trials on colorectal cancer with the guaiac fecal occult blood test: the impact on incidence and mortality of colorectal cancer

	% colonoscopy	*Reduction mortality*	*Reduction incidence*
Minnesota Trial (31-33)	38%	33%	20%
Nottingham Trial (34, 35)	1.9%	13%	0%
Funen Trial (36, 37)	5.3%	11%	0%
Burgondy Trial (38)	3.7%	16%	0%

this period, but less than the incidence. A screening policy with FOBT, and opportunistic colonoscopy was introduced in 1992; since this date the mortality rate is stabilized (39–43). The impact of having colorectal cancer on life expectancy of persons aged 50 years or more has been estimated in a Markov analysis (44): this impact is at the highest in the younger age group (50–54 years) where colorectal cancer decreases the life expectancy by 282 days. The gain ensured by a policy of screening has also been estimated in the analysis; in the same age group (50–54 years) screening extends expected lifetime by 51 days using FOBT, 86 days using sigmoidoscopy, 170 days using colonoscopy.

Impact on All Causes Mortality

In spite of the impact on specific mortality from colorectal cancer an impact on mortality "all causes" should not be expected. The proportion of deaths from colorectal cancer among all causes of death is not more than 2% or 3% (Table 4). In the 13 years follow-up of the Norwegian trial (45) after flexible sigmoidoscopy and polypectomy in persons with "positive" findings, the global proportion of "death all causes" was similar among persons treated for polyps and the others. In the Minnesota randomized trial with FOBT (31–33) higher mortality rates from ischemic heart disease occurred in the screened group because the cause of death has been shifted from colorectal cancer to heart disease for some persons. A systematic analysis of the relative risk for death was made in the cumulative data of three randomized trials analyzed in the Cochrane review on FOBT (46). The analysis involved 245,217 persons with 2,148 deaths from colorectal cancer: the decrease of the risk of death from colorectal cancer in the screened persons was confirmed (Odds ratio: 0.87). On the other hand in the same persons the relative risk of non-RC death from other causes increased slightly (Odds Ratio:1.0). The variation of the mortality unrelated to colorectal cancer balanced that of mortality from colorectal cancer; the impact on global mortality was nil.

Impact on Incidence of Colorectal Cancer

The incidence of colorectal cancer is not influenced by screening with FOBT; while it decreases with endoscopic screening through the endoscopic resection of precursors. In countries having a well established policy combining organized screening with FOBT and opportunistic screening with colonoscopy a decreasing time trend of the ASR incidence is shown in cancer registries. In the USA, during the period 1975–2003, the SEER Registries (3) show a 19.4% decrease of the incidence rate. The origin of the variation is found in

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Table 4.
Mortality in the USA in 2002: proportion of deaths from colorectal cancer for all ages and in three age groups.

	All Ages	*45–54*	*55–64*	*65 +*
Deaths all causes N°	2,443,387	172,385	253,342	1,811,720
Deaths Colorectal Cancer N°	59,300	4,500	8,900	44,200
% total	2.4%	2.6%	3.5%	2%

Sources: All causes of deaths: US mortality data in National Center for Health Statistics , table GMWK23F. Estimated numbers of deaths from colorectal cancer: Globocan 2002 database

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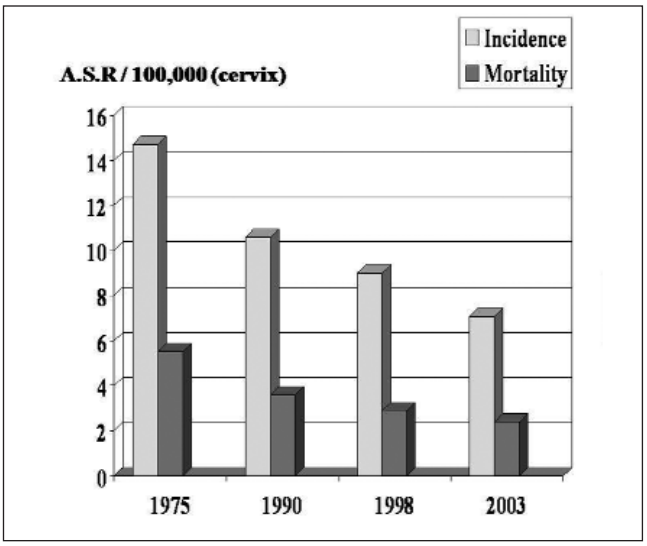

Figure 1. Age adjusted incidence and mortality rates per 100,000 persons for cancer of the cervix during the period 1975–2003. All ages, all races, women. Adjustment to the 2000 US population. The incidence decreased from 14.1 in 1975 to 7.1 in 2003. A similar decrease occurred for mortality (from 5.5 to 2.4) *Source: Incidence rates from SEER 9 registries. Total mortality rates in the US population.*

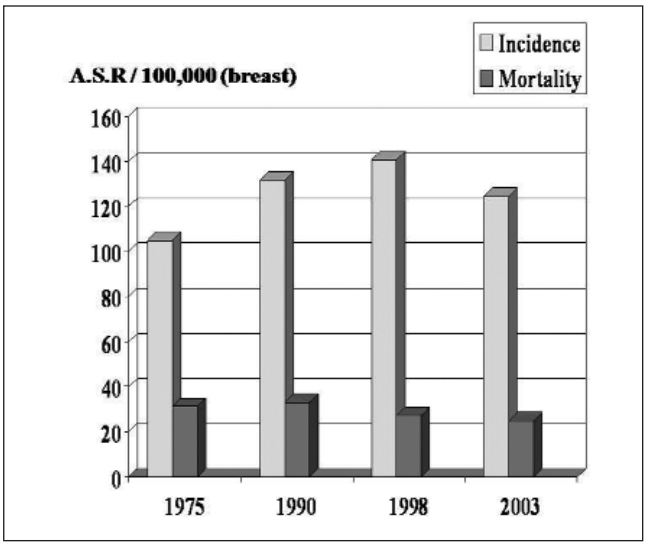

Figure 2. Age adjusted incidence and mortality rates for breast cancer during the period 1975-2003. All ages, all races, women. Adjustment to the 2000 US population. The incidence increased from 105.0 in 1975 to 124.7 in 2003 (with a peak at 140.8 in 1990). During the same period the decrease in mortality was minimal (from 31.4 to 25.1) *Source: Incidence rates from SEER 9 registries. Total mortality rates in the US population.*

the diffusion of endoscopic treatment and resection of precursors, and in probable changes in the environmental factors. In Japan, the risk of colorectal cancer increases since 1975 in the statistics with a sustained progression of the ASR incidence. A screening policy with FOBT, and opportunistic colonoscopy was introduced in 1992; since this date the incidence rate tends to be stable, suggesting an impact of the endoscopic resection of precursors (39–43).

Legitimacy of Screening for Cancer

Evidence Based Medicine aims to use reliable criteria in the evaluation of diagnostic and therapeutic procedures. In the meta-analyses of the Cochrane databases the demonstration of evidence relies mostly, but not only, on randomized trials; the reviews include recommendations on the clinical indications of procedures or strategies. Databases on the prevention of cancer through early detection and treatment have been published for breast cancer, prostate cancer and colorectal cancer. The criteria used in the meta-analyses are the impact on incidence and mortality, risk of complications, over-diagnostic and over-treatment, compliance, and quality of life. Those meta-analyses aim to explore whether there is a robust evidence to recommend screening. The meta-analyses aims to answer whether the benefit is more than harmful effects, and whether the intervention is worth the cost.

The conclusions of the Cochrane meta-analyses apply to a generalized policy of cancer prevention through early detection (organized screening). The limits for the legitimacy of screening, given by the "evidence" methodology, should not be extended to individual situations of opportunistic screening. In this situation, non-quantifiable parameters of reassurance play a large role.

The Cochrane database on mammography and screening for breast cancer (11) estimates that screening ensures a 15% reduction of the relative risk for breast cancer mortality; screening also leads to over-diagnosis and over-treatment. Some healthy women, will be treated unnecessarily (lumpectomies and mastectomies). It is concluded that it is not clear whether

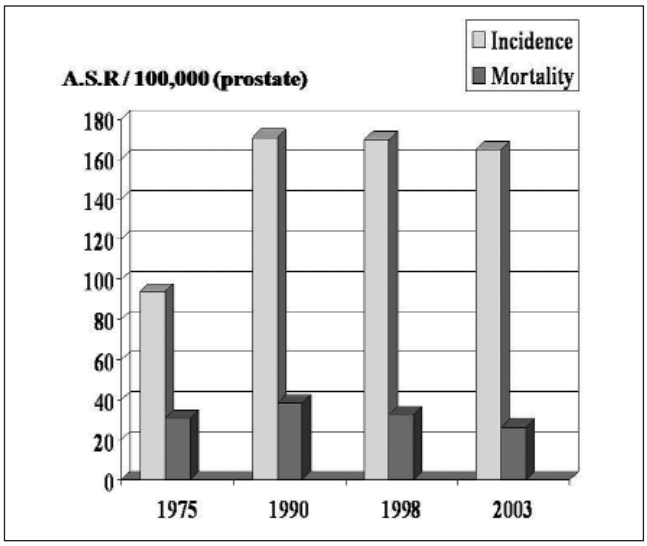

Figure 3. Age adjusted incidence and mortality rates for prostate cancer during the period 1975–2003. All ages, all races, men. Adjustment to the 2000 US population. The incidence increased from 94.0 in 1975 to 164.8 in 2003. During the same period the decrease in mortality was minimal (from 30.9 to 26.5) *Source: Incidence rates from SEER 9 registries. Total mortality rates in the US population.*

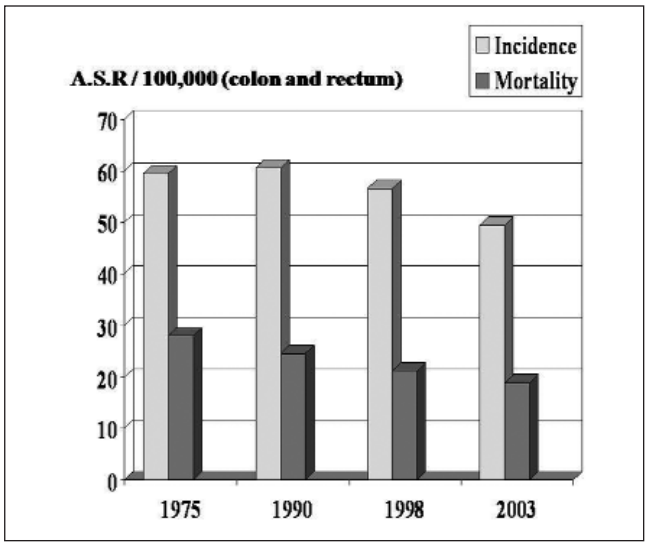

Figure 4. Age adjusted incidence and mortality rates for colorectal cancer during the period 1975–2003. All ages, all races, men and women. Adjustment to the 2000 US population. The incidence began to decrease slightly after 1990. The respective values were 60.6 in 1990 and 49.5 in 2003. The mortality decreased regularly during this period from 28.0 in 1975 to 18.9 in 2003. *Source: Incidence rates from SEER 9 registries. Total mortality rates in the US population.*

screening does more good than harm and that invited women should be fully informed of both benefits and harms. The role of over-diagnosis is also confirmed by the increased incidence of cases of breast cancer in registries following a policy of screening as shown in Australia (47) and in the statistics of the "Institut de Veille Sanitaire" in France. The Cochrane database on PSA antigen and screening for prostate cancer (13) concludes that there is no robust evidence from randomized controlled trials, to either support or refute the routine use of mass, selective or opportunistic screening for reducing prostate cancer mortality. It is concluded that more results are required to make evidence-based decisions. The Cochrane database on FOBT and screening for colorectal cancer (12) based on the meta-analysis of randomized trials estimates that screening ensures a reduction in colorectal cancer mortality of 16%. The amount of reduction reaches 23% when it is adjusted for individual attendance to screening. The benefit of screening also includes a possible reduction in cancer incidence through removal of colorectal adenomas and potentially less invasive surgery. Harmful effects of screening are the complications of colonoscopy, stress and discomfort of procedures, and the anxiety caused by false positive filter tests. It is concluded that more information is needed before widespread screening can be recommended.

The evolution of the ASR Incidence and Mortality curves (time trends) for a cancer, during the years following the introduction of a generalized policy of prevention through organized and individual screening is a representative index of its efficacy. Data are selected from cancer registries for Incidence and from national Vital Statistics for Mortality. Curves may show distinct, or eventually diverging slopes, as shown in the comparison of data in the SEER registries and in National Vital statistics in the USA (Figures 1–4): for cancer of the Uterine Cervix both mortality and incidence decrease—for breast cancer the divergence between increased incidence and stable mortality suggest that there is over-detection for the less evolutive cases—for prostate cancer a considerable increase in incidence points to a considerable amount of over-

detection while mortality increases slightly—for colorectal cancer incidence and mortality decrease; the more pronounced slope of the mortality curve results from detection at a more early stage and improved treatment.

CONCLUSIONS

The conventional protocol of screening for colorectal cancer is based on a FOBT filter test with a upper proportion of "positive" responses in 4%. The persons tested as "positive" are then submitted to colonoscopy. According to criteria of Evidence Based Medicine a small reduction of the specific mortality from colorectal cancer (not more than 15%) occurs in the group proposed screening, without impact on global mortality. Screening has had no impact (neither increase , nor decrease) on the number of incident cases. Selective results are improved for the persons compliant to screening and its repeated campaigns; then the reduction in mortality is higher and there is a reduction in incidence.

The impact of a generalized screening policy which combines organized screening with the FOBT and the increasing practice of individual screening with primary colonoscopy, is shown in the time trends of cancer registries and of Vital statistics of the country: there is a slight decrease in the incidence, and mortality rates from colorectal cancer. Overall the legitimacy and the cost/efficacy ratio of screening for colorectal cancer are comparable to that of screening with mammography for breast cancer with the advantage that there is no over-diagnosis of cancer and no increase in the incidence of cases.

The development of primary screening with endoscopy will increase the impact of screening on the incidence, and specific mortality from colorectal cancer. Endoscopy is still the gold standard procedure of detection of early cancer and precursors, however if polypoid adenomas are easily detected, nonpolypoid adenomas which play a significant role as the precursors of advanced cancer are still often missed. This situation deserves to be urgently improved through the training of endoscopists. A potentially harmful consequence of the increased diffusion of opportunistic screening with endoscopy is over-diagnosis and over-treatment of benign neoplastic precursors with no potential of progression with consequences on morbidity and complications. ■

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