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Age-dependent shift-to-the-right in the localization of colorectal adenomas

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Summary. The age-dependent prevalence and topographical distribution of colorectal adenomas was investigated in 1006 unselected autopsies (554 males and 452 females) in Mainz, FRG. In 200 out of 1006 autopsies (19.8%) a total of 498 adenomas of the large intestine were detected. The percentage of patients with adenomas increased continuously with age. Only 6% of all adenomas were localized in the caecum and 8% in the rectum, whereas all the other adenomas were distributed rather evenly throughout the ascending colon (23%), the transverse colon (25%), the descending colon (15%) and the sigmoid colon (23%). Analyzing the topographical distribution of adenomas for definite age groups (40–59, 60–69, 70–79 and 80–99 years of age), it became evident that the topographical distribution is not constant, but shows an age-dependent shift-to-the-right, i.e. with advancing age an increase in the relative frequency of adenomas in the proximal colonic segments (from caecum to transverse colon) and a decrease in the distal segments (from descending colon to rectum). This shift to the right, which evolves continuously from the youngest to the oldest age group, results from a disproportionate increase in the absolute number of adenomas in the proximal colonic segments when compared with the distal segments. The age-dependent shift-to-the-right of colorectal adenomas provides an important confirmation of the adenoma-carcinoma sequence, but cannot be explained by current concepts concerning the aetiology of colorectal adenomas and carcinomas.

Key words: Adenoma – Colorectal – Prevalence – Topographical distribution – Colorectal carcinoma

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Introduction

In recent years there have been many reports on changing site distribution of colorectal carcinomas ("upward migration") resulting in an increasing porportion of proximal relative to distal carcinomas (Axtell et al. 1966; Beart et al. 1983; Cady et al. 1974; Franklin et al. 1970; Lanier et al. 1973; Liechty et al. 1968; Mamazza et al. 1982; Rhodes et al. 1977; Rosato et al. 1981; Snyder et al. 1977). This distribution pattern raises new questions concerning the localization of adenomas as the most important precancerous lesions of the large intestine (Morson et al. 1983). Because most adenomas remain clinically asymptomatic during lifetime, investigations based on biopsy or surgical material sampling suffer from a heavy preselection bias, presumably overemphasizing the importance of distal adenomas (Day 1982). Therefore, autopsy studies remain the more reliable source of information on their topographic distribution.

Material and methods

During a period of two years 1006 unselected autopsy cases were examined for large intestinal adenomas at the Department of Pathology of the University Hospital in Mainz, FRG. This study included 552 males and 454 females, aged from 15 years to 99 years. By reference to the clinical files previous endoscopic or surgical removal of adenomas during life was excluded in all cases.

Following the recommendations of Day (1982) and Eide and Stalsberg (1978) the large intestine was always inspected by the same pathologist. The localization of every polypoid lesion was determined according to the proposals of Correa et al. (1977) and Rickert et al. (1979). In brief, the distance of each adenoma from the most proximal point of the caecum was recorded in centimeters. This distance was then related to the total length of each large intestine. Thus, the localization of each adenoma was determined by the relative distance from the most proximal point of the caecum, allowing a comparison of adenoma localization in intestines of different absolute length. An assignment of each adenoma to conventional colonic

segments was possible by defining the length of each colonic segment in relative terms. According to the proposals of Correa et al. (1977) and Rickert et al. (1979), 5% of the total colonic length was attributed to the caecum, 28.5% to the transverse colon, 9.5% to the caecum and 19% each to the ascending colon, the descending colon and the sigmoid colon. Every polypoid lesion detected was classified histologically according to the WHO-classification. For each adenoma, the size and histological type as well as the age and the sex of the adenoma carrier were recorded separately. Due to the progressive autolysis of many adenomas an attribution to the different grades of atypia was omitted.

Results

In 200 out of 1006 autopsies (19.8%) a total of 498 large bowel adenomas were detected (Table 1); there were 88 patients with solitary and 112 patients with multiple adenomas. No significant differences in the sex distribution could be demonstrated, the sex ratio being 1:1.01 male to female.

The frequency of patients with adenomas steadily rose from 6% in the age group of 40–49 years to 38.5% in the age group of 90–99 year old patients (Fig. 1). A correspondent age-dependent increase emerged for patients with multiple adenomas, whose frequency increased from 3% in the youngest age group to 23% in the oldest age group (Fig. 1). With the exception of a single adenoma in an 18 year old male no adenomas could be detected in persons younger than 40 years of age.

Histologically, 9 (2%) adenomas were classified as purely villous, 106 (21%) as tubulo-villous, and 383 (77%) as tubular. Considering the size of adenomas in relation to the histological type, it became evident that adenomas with a villous component tended to be larger than the purely tubular adenomas: Only 0.8% of the tubular adenomas exceeded 2 cm in diameter, the vast majority (91%) being smaller than 1 cm in diameter. On the other hand, 47% of the adenomas with a villous component were greater than 1 cm in diameter and 15% even exceeded 2 cm in diameter.

Considering the topographical distribution without special regard to the age of the adenoma patients, only 6% and 8% of all adenomas were localized in the caecum and the rectum respectively, whereas all the other adenomas were distributed rather evenly throughout the ascending (23%), transverse (25%), descending (15%) and sigmoid colon (23%).

In analyzing the topographical distribution of adenomas for definite age groups (40–59, 60–69, 70–79 and 80–99 years of age), the percentage of adenomas in the different colonic segments was calculated separately for each age group (Fig. 2).

Table 1. The absolute number of autopsies, patients with adenomas, and adenomas in the different age-groups

Age group	Number of autopsies	Number of patients with adenomas	Number of adenomas
15–39	70	1	1
40–59	250	29	72
60–69	235	49	108
70–79	316	78	167
80–99	135	43	150
	1006	200	498

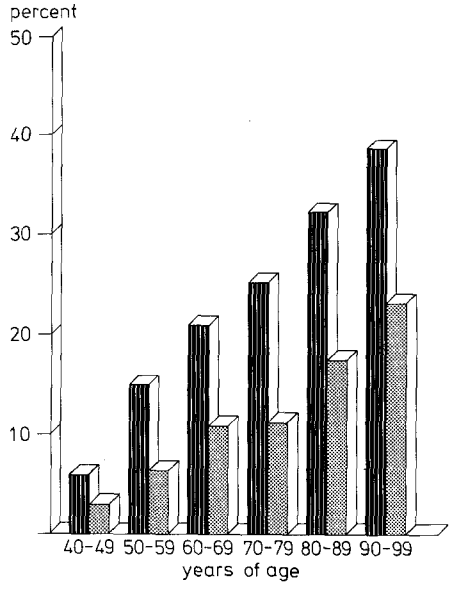

Fig. 1. Percentage of adenoma patients in the different age groups. ▥ patients with solitary and multiple adenomas; ▩ patients with multiple adenomas

Comparing the percentage of adenomas localized at a definite colonic segment, it appeared that with increasing age the relative frequency of adenomas increased in the caecum, the ascending colon and the transverse colon (i.e. the proximal parts of the large intestine) and simultaneously decreased in the descending colon, the sigmoid colon and the rectum (i.e. the distal parts of the large intestine).

To be sure that these adverse trends of the relative frequency of adenomas were not artificially imposed by cases with multiple adenomas, the topographical distribution of the solitary adenomas was similarly analyzed. Due to the limited number of only 87 solitary adenomas, this comparison was confined to two age groups (40–69 and 70–99 years of age). As shown in Fig. 3, a corresponding trend was also demonstrated for solitary adenomas, the

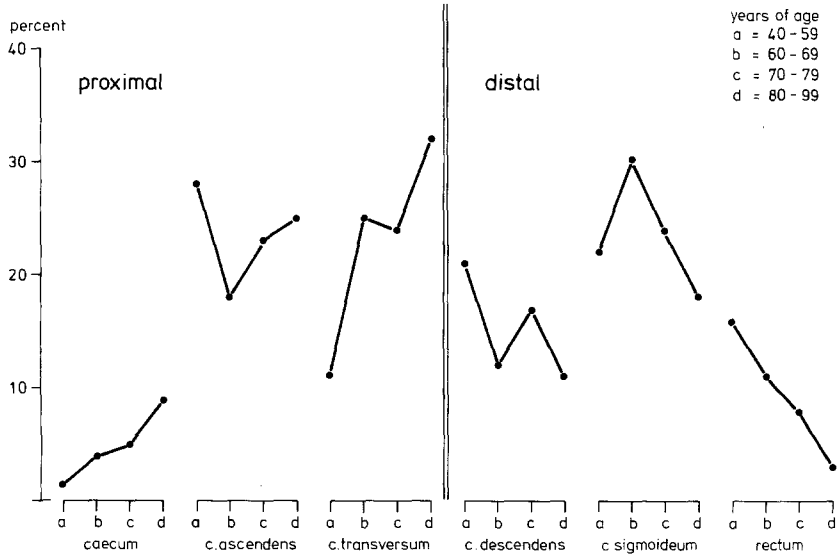

Fig. 2. Age-related topographical distribution of all adenomas ($n=498$) in percent

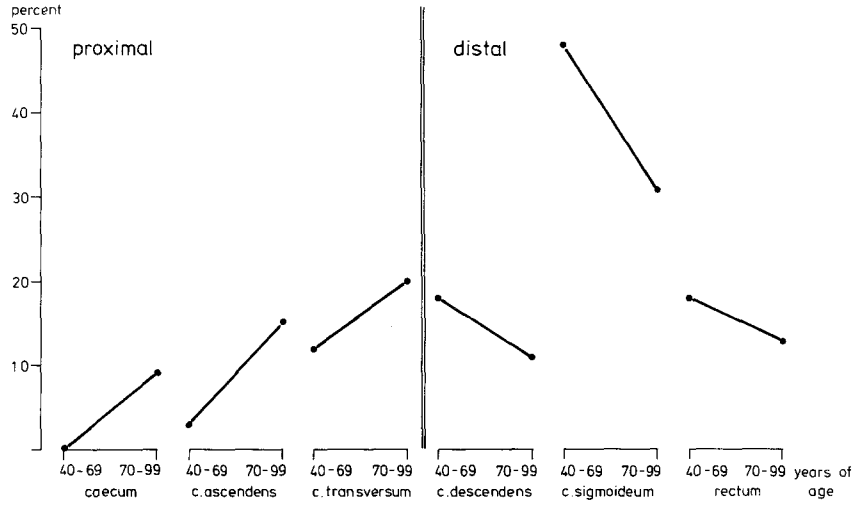

Fig. 3. Age-related topographical distribution of the solitary adenomas ($n=87$) in percent

relative frequency of which rose with age in the proximal segments and declined in the distal segments.

An age-dependent variation of the topographical distribution was also demonstrated by examining the ratio of the number of adenomas in the proximal colonic segments to the number of adenomas in the distal segments (Fig. 4). Calculating this ratio separately for the different age groups (40–59, 60–69, 70–79 and 80–99 years of age) it was shown that the ratio increased continuously with advancing age; it was less than 1 in the younger age groups, indicating a predominance of adenomas in the distal colonic segments, whereas the ratio was greater than 1 in the older age groups, indicating a predominance of adenomas in the proximal colonic segments.

For a direct comparison of the frequency of adenomas in absolute terms, the number of adenomas detected in our autopsy cases was extrapolated to 1000 autopsies in each age group (40–59, 60–69, 70–79, 80–99 years of age), correcting this way the varying number of autopsies in the different age groups. Based on these extrapolated numbers (Fig. 5), it can be demonstrated – with the exception of the rectum – that the absolute number of adenomas increases with age in all colonic segments, this increase being most pronounced in the proximal segments of the colon.

The analysis of adenoma distribution was completed by a calculation of the adenoma density, taking into account the different length and surface area of the various colonic segments. According to the proposals of Correa et al. (1977) and Rickert

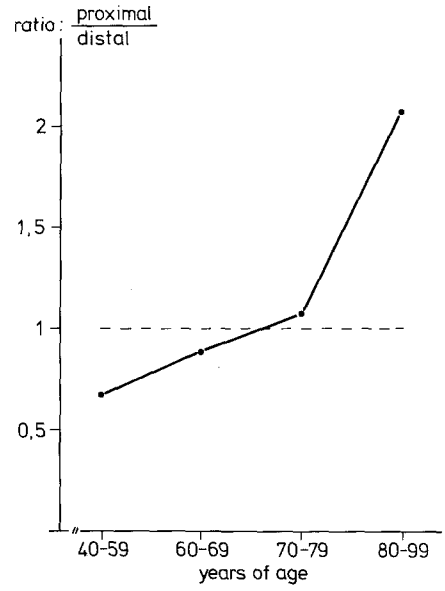

Fig. 4. Age-related ratio of the adenomas in the proximal and distal large intestinal segments

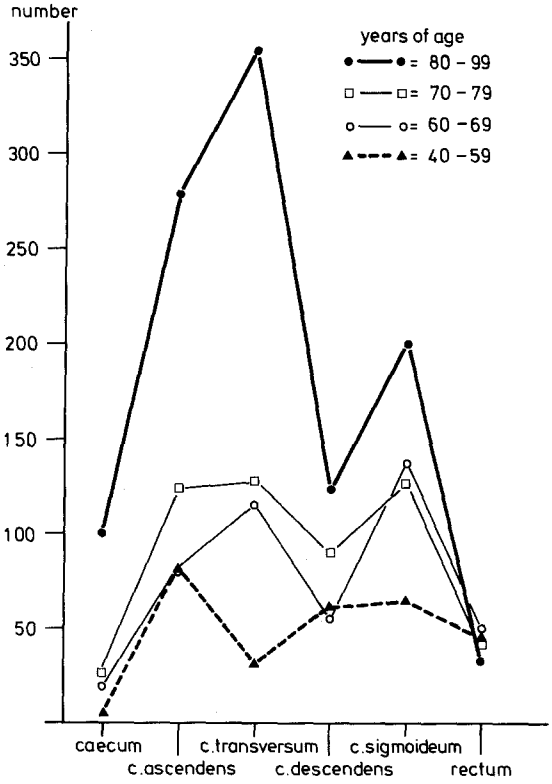

Fig. 5. Age-adjusted topographical distribution of adenomas in absolute numbers after extrapolating the adenoma number for 1000 autopsies in each age group

et al. (1979) the length and surface area of the different colonic segments were defined in relative terms, as before 5% caecum, 28,5% transverse, 9.5% rectal and 19% each to ascending, descending and sigmoid colon. Based on the extrapolated

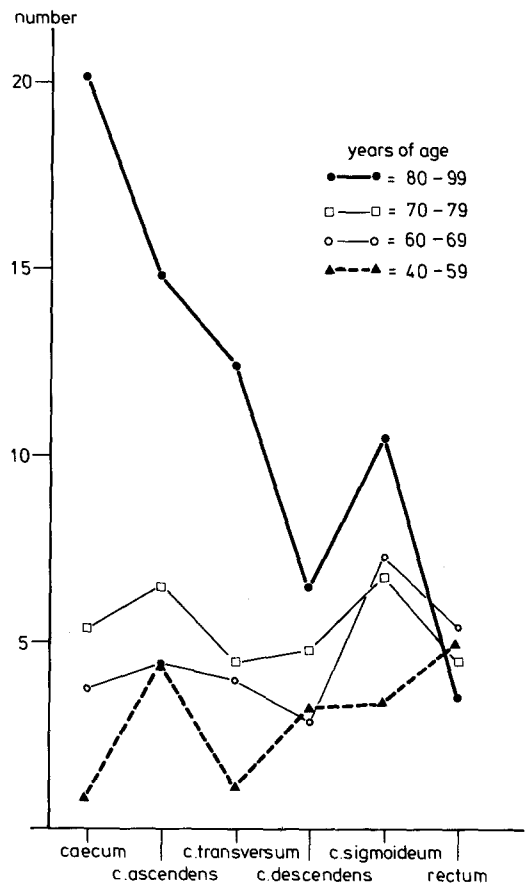

Fig. 6. Age-adjusted adenoma density (=absolute number of adenomas per 1% surface area) in the different intestinal segments after extrapolating the adenoma number for 1000 autopsies in each age group

numbers of adenomas presented in Fig. 5, the adenoma density in the different colonic segments was calculated as the number of adenomas per 1% of the total colonic surface area. Fig. 6 shows that the adenoma density rises from the caecum to the rectum in the youngest age group (40 to 59 years of age). This increase, however, slows down in the following age groups and finally shows an inversion in the oldest age group (80 to 99 years of age), the density now declining from the caecum to the rectum. That is to say in the youngest age group the adenoma density is highest in the rectum, whereas in the oldest age group the adenoma density is highest in the caecum.

Discussion

It is clearly evident from our autopsy study that the topographical distribution of adenomas shows an age-dependent shift to the right, the relative frequency of adenomas increasing with age in the proximal segments and simultaneously decreasing

in the distal segments. This shift to the right, which evolves continuously from the youngest to the oldest age group, results from a disproportionate increase of the number of adenomas in the proximal segments when compared with the number of adenomas arising in the distal segments.

The evaluation of this age-dependent shift to the right requires the exclusion of an artificial bias. First of all, the possibility had to be rejected that the proposed shift was artificially induced by a sampling error, comparing predominantly solitary adenomas in the younger age group with predominantly multiple adenomas in the older age group. That is to say, the shift to the right may be the effect of increasing occurrence of multiple adenomas rather than the effect of advancing age. We therefore analyzed the relation between age and the occurrence of solitary and multiple adenomas respectively by the chi-square method. The resulting p-value of 0.58 rejects the possibility of a sampling error, clearly indicating that in our sample there is no relation between the age of the patients and the multiplicity of adenomas. Furthermore, the age-dependent shift to the right could be demonstrated not only for all adenomas (solitary and multiple), but also for solitary adenomas alone (Fig. 3). An unintended preselection bias caused by a recto-sigmoideoscopic removal of predominantly distal adenomas during the lifetimes of our adenoma patients was excluded by reference to the clinical files.

Provided that adenomas are the most important precancerous lesion of the colon (Enterline 1978; Hill 1978; Morson et al. 1983; Muto et al. 1975), the topographical distribution of adenomas and carcinomas should be congruent. However, disparities of adenoma and carcinoma distribution have been demonstrated by many investigators. So the great majority of all large bowel carcinomas in high-risk populations arise in the distal colonic segments (DeJong et al. 1972; Haenszel and Correa 1971; Snyder et al. 1977), whereas colonic adenomas are rather evenly distributed throughout the proximal and distal segments as demonstrated by many autopsy studies (Arminski et al. 1964; Chapman 1963; Coode et al. 1985; Eder 1978; Eide et al. 1978; Rickert et al. 1979; Sato et al. 1976; Williams et al. 1982). The resulting inconsistency has partly been resolved by taking into account a different malignant potential of adenomas, which varies with size, degree of atypia and villosity (Morson et al. 1983; Muto et al. 1975). However, with rare exceptions (Blatt 1961; Eide et al. 1978) most autopsy studies do not pay any attention to the relationship between age and adenoma localization. In fact, adenomas are not evenly distributed throughout the large intestine, if their topographical distribution is related to the age of patients. Our investigation clearly demonstrates an age-dependent variation of localization with a distal predominance of adenomas in the youngest age groups (Fig. 4). With regard to the latency period usually required for the progression to invasive cancer (Enterline 1978; Muto et al. 1975), a congruence between the distal predominance of adenomas and carcinomas becomes evident. Therefore, we think, it is the distal concentration of adenomas in younger age groups that explains the distal concentration of large intestinal carcinomas.

Furthermore, our autopsy study indicated that the predominance of adenomas in the distal colon is subjected to a continuous shift to the right with advancing age, finally resulting in a proximal predominance of adenomas in old age (Fig. 4). According to this observation, colorectal carcinomas should also exhibit a corresponding age-dependent shift to the right, i.e. a disproportionate increase of the proximal carcinoma incidence with advancing age. The verification of this postulate was difficult, because reports on the incidence rates of colorectal carcinomas specified by both age and subsites are extraordinarily sparse. Thus, the data presented by Snyder et al. (1977) in their comprehensive review of 40,791 colorectal carcinomas proved to be the only appropriate source of information were are aware of. In Table 2 the age-specific incidence rates presented by Snyder et al. (1977) were tabulated in a modified arrangement, calculating the ratio of proximal to distal incidence rates separately for each age group (i.e. 40–64 and older than 65 years of age) and for each time period. It is evident that within every time period from 1940–1973 the ratio in old age permanently exceeded the ratio in the younger age group. These data indicate a disproportionate increase of proximal carcinoma incidence with advancing age, corresponding to the disproportionate increase in the number of adenomas demonstrated by our investigation. Therefore, the age-dependent shift to the right af adenomas and hence carcinomas emerges as an important confirmation of the adenoma-carcinoma-sequence.

The age-dependent shift demonstrated by our investigation must not be confused with recent reports on a secular change of the topographical distribution of colorectal carcinomas (Axtell et al. 1966; Beart et al. 1983; Cady et al. 1974; Franklin et al. 1970; Lanier et al. 1973; Liechty et al. 1968; Mamazza et al. 1982; Rhodes et al. 1977; Rosato

Table 2. Age-specific incidence rates per 100000 females (**A**) and males (**B**) of colorectal carcinomas for the time period 1940–1973, modified according to Synder et al. (1977)

A

Time period	1940–1944		1945–1949		1950–1954		1955–1959		1960–1964		1965–1969		1970–1973	
years of age	45–64	+65	45–64	+65	45–64	+65	45–64	+65	45–64	+65	45–64	+65	45–64	+65
Proximal (c. ascendens, c. transversum)	16.4	51.9	21.5	78.7	24.4	83.7	21.4	98.2	22.3	115.7	24.0	122.0	22.7	127.4
Distal (c. descendens, c. sigmoideum, rectum)	44.5	132.0	56.3	143.4	61.4	154.2	59.8	169.9	56.6	160.7	55.4	168.7	58.7	172.2
Ratio: proximal / distal	0.369 < 0.393		0.382 < 0.549		0.397 < 0.543		0.358 < 0.579		0.394 < 0.720		0.433 < 0.723		0.387 < 0.740	

B

Time period	1940–1944		1945–1949		1950–1954		1955–1959		1960–1964		1965–1969		1970–1973	
years of age	45–64	+65	45–64	+65	45–64	+65	45–64	+65	45–64	+65	45–64	+65	45–64	+65
Proximal (c. ascendens, c. transversum)	16.4	51.7	18.0	60.3	18.8	82.7	19.4	95.5	21.0	110.1	23.5	122.9	22.1	145.8
Distal (c. descendens, c. sigmoideum, rectum)	54.1	180.0	65.3	203.6	64.6	225.5	63.3	241.9	62.9	251.2	59.8	285.3	71.1	284.5
Ratio: proximal / distal	0.303	0.287	0.276 < 0.296		0.291 < 0.367		0.306 < 0.395		0.334 < 0.438		0.393 < 0.431		0.307 < 0.512	

et al. 1981; Snyder et al. 1977). These investigations deal with an upward migration of colorectal carcinomas in recent decades resulting in a rising proportion of proximal carcinomas relative to the proportion of distal carcinomas. However, a critical review reveals that these investigations do not refer to an age-dependent variation of localization, but only describe a secular trend based on the comparison of distribution patterns between different populations at varying time periods. Furthermore, only few reports (Axtell et al. 1966; Beart et al. 1983; Cutler 1969; Snyder et al. 1977) present incidence rates, which are indispensable for a further analysis of this phenomenon. In any case secular fluctuations of carcinoma incidence must be interpreted cautiously, because incidence rates are affected by a host of often imponderable factors (Greenberg et al. 1982; Lanier et al. 1973). First of all, to evade the pitfalls of different age structures in the populations compared (Greenberg et al. 1982) only reports presenting age specific incidence rates can be an appropriate reference. Again it is only Snyder et al. (1977), who meet these prerequisites and confirm that the upward migration of large intestinal carcinomas is not artificially imposed by differing age structures of the populations compared. Next to this, the age-dependent shift demonstrated by our investigation raises the question of whether the secular upward migration of carcinomas might result from an improved availability of refined diagnostic and therapeutic techniques for older patients (Greenberg et al. 1982; Haenszel and Correa 1971; Lanier et al. 1973; Rosato et al. 1981). As emphasized by Greenberg et al. (1982), it is the elderly patient who was less likely to be diagnosed accurately in the past and has greatly increased his utilization of medical care in recent decades. This might have led to a marked reduction of the "underdiagnosis rate" (Berg et al. 1970) in old age and to a closer approximation to the real distribution pattern of colorectal carcinomas. This view is strongly sup-

ported by the age-specific incidence rates presented by Snyder et al. (1977, Table 2), which suggest that the most decisive impact on the secular upward migration of colonic carcinomas results from the disproportionate increase in the incidence of proximal carcinoma in old age. However, it is this disproportionate increase which denotes the age-dependent shift to the right proposed by our investigation. The upward migration of large intestinal carcinomas observed in recent decades is therefore explained by but not synonymous with the age-dependent shift to the right of carcinomas.

Most aetiological models agree that dietary factors are important for colonic carcinogenesis (Correa et al. 1977; DeJong et al. 1972; Hill 1978, 1983; Palmer et al. 1983; Parkash 1974; Weisburger et al. 1982; Wynder and Reddy 1974; Zaridze 1983), but there is less unanimity on the specific nature of these factors. Nevertheless, the distal predominance of colorectal carcinomas (DeJong et al. 1972; Haenszel and Correa 1971; Snyder et al. 1977) in high-risk populations strongly indicates a directional process. The supposed carcinogens and co-carcinogens seem to gain in effectiveness from the caecum to the rectum. This effect is primarily related to a concentration gradient (Haenszel and Correa 1971; Parkash 1974) resulting from the continuous dehydration of the faeces from the caecum to the rectum. Furthermore, the large intestinal bacterial flora and its metabolic conversion of certain faecal components into carcinogens or co-carcinogens supposedly lead to a distal accumulation of these substances (Bresnick 1980; Correa et al. 1977; Hill 1978). The effects of increasing concentrations of carcinogens or co-carcinogens are assumed to be further modified by the faecal transit time (DeJong et al. 1972; Parkash 1974), determining the effective exposure of mucosal epithelia. However, hypotheses concerning the causal pathogenesis of colorectal carcinomas were primarily formulated without regard to the precursor lesion. Consequently, there is only little reflection on the effects of dietary factors on the different stages of the adenoma-carcinoma-sequence, namely adenoma formation, adenoma growth, and progression to invasive growth (Hill 1978; Morson et al. 1983). Nevertheless, the general principles of an environmentaly induced tumorigenesis – i.e. the concentration and time-dependence of effective exposure – should also be applicable to large intestinal adenomas. The sub-site risk for the development of adenomas can be evaluated more accurately after a calculation of the adenoma density. In accordance with a concentration gradient of tumorigenic factors already proposed for colorectal carcinomas, the adenoma density increases from the caecum to the rectum in the age group of 40–59 year old patients. However, the progressive inversion of adenoma density with advancing age (Fig. 6) and thus the age-dependent shift to the right of adenomas obviously contradict the current concepts of tumorigenesis, which assumes a concentration gradient culminating in the rectum. In this context, it seems noteworthy that Haenszel et al. (1971), reporting on a predominance of proximal carcinomas in low-risk populations and on a distal predominance in high-risk populations, theorized that proximal and distal carcinomas might have "related but not identical aetiologies". Beart et al. (1983) speculated that proximal and distal carcinomas of the large bowel might be biologically separate cancers, which either respond to different risk factors or respond differently to the same risk factors. The age-dependent shift to the right of adenomas and hence carcinomas might therefore result from an age-dependent changing exposure to undefined risk factors or from an age-dependent changing susceptibility of mucosal epithelia. In any case, the current concepts concerning the causal pathogenesis of colorectal adenomas and carcinomas should be reassessed with respect to the age-dependent shift to the right.

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