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National Polyp Study data: evidence for regression of adenomas

Abstract

Objectives

The data of the National Polyp Study, a large longitudinal study on surveillance of adenoma patients, is used for testing assumptions on the adenoma-carcinoma sequence.

Methods

The observed adenoma and colorectal cancer incidence in the National Polyp Study were compared with the simulated outcomes of the MISCAN-COLON model of epidemiology and control of colorectal cancer for the United States population based on expert opinion. Variants of this model were explored in order to identify assumptions on the adenoma-carcinoma sequence that are consistent with the study observations.

Results

The high observed adenoma detection rates at surveillance and low observed colorectal cancer incidence in the National Polyp Study could only be explained by assuming a high incidence rate of adenomas accompanied by regression of adenomas.

Conclusions

The National Polyp Study data suggest that adenoma prevalence results from a dynamic process of both formation as well as regression of adenomas. This lowers the expectations for the effects of colorectal cancer screening strategies that focus on adenoma detection.

Introduction

The evolution of colorectal cancer from a precursor lesion, the adenoma, was first reported in studies from St. Mark's Hospital in London and later designated by Morson and coworkers as the adenoma-carcinoma sequence [Morson 1976, Morson 1984]. Morson stated that the evolution of cancer from adenomas takes at least five years and may be more than 20 years [Morson 1976]. Introduction of colonoscopy provided an opportunity for clarifying this sequence because of its ability to examine the entire colon and remove polyps for pathological examination. These pathology studies have in recent years been correlated with molecular genetic studies [Vogelstein 1988]. The adenoma-carcinoma sequence is now well established as the major pathway for the development of colorectal cancer in the general population and in high risk patients in families with Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC) [Muto 1975, Morson 1984]. The epidemiology and natural history of adenomas are not only important for choosing the optimal follow-up policy after polypectomy, but also for evaluating endoscopic screening for colorectal adenomas and cancer. A better understanding of the dynamics of the adenoma-carcinoma progression would further clarify what can be expected of various colorectal cancer screening strategies that involve adenoma detection.

The National Polyp Study was a longitudinal study that provided prospective data on the adenoma-carcinoma sequence and the effect of colonoscopic polypectomy. It was organized in 1978 and began to accrue patients in 1980. Its purpose was to evaluate more frequent and less frequent follow-up surveillance intervals in patients in whom newly diagnosed adenomas were removed. Removal of these adenomas resulted in a colorectal cancer incidence that was markedly lower than expected without polypectomy. In this report we present a study of the natural history of the adenoma-carcinoma sequence, applying a micro-simulation model for colorectal cancer epidemiology and control (MISCAN-COLON) [Loeve 1999] to the data of the National Polyp Study.

Material and methods

The National Polyp Study data

The National Polyp Study was a randomized controlled trial of colonoscopic surveillance in patients who have had at least one adenoma removed [Winawer 1993b]. All patients referred for colonoscopy or polypectomy between November 1980 and February 1990 in seven participating centers who did not have a family or personal history of familial polyposis, inflammatory bowel disease, or a personal history of polypectomy or colorectal cancer were eligible for enrollment in the study. A total of 9112 subjects referred for colonoscopy were candidates for the study. Of these, 4763 were excluded because no polyps were found. Other excluded subjects were 776 with non-adenomatous polyps only, 549 with colorectal cancer, 149 with inflammatory bowel disease or other conditions, and

35 with a sessile adenoma with a base larger than 3cm. Patients with incomplete initial examinations were also excluded (n=208). The colon had to be cleared with 3 examinations or within 3 months for the patient to be part of the study. Of the 2632 eligible patients, 1418 patients consented to participate and were randomized to one of two arms. All detected polyps were removed and a surveillance colonoscopy was offered in Arm A at 1, 3 and 6 years after initial colonoscopy and in Arm B at 3 and 6 years after initial colonoscopy. If the colon was not cleared with high confidence at surveillance colonoscopy, the patient was scheduled for repeat colonoscopy. Mean follow-up time was 5.9 years. Five cancers were found during the trial (C. I. 1.6-11.7) (2 in arm A and 3 in arm B), while 21 were expected based on the U.S. population with the same age and sex distribution [Winawer 1993a], and 43 to 48 were expected based on a comparison with two polyp bearing cohorts without intervention [Stryker 1987, Atkin 1992]. All five cancers were asymptomatic malignant adenomas detected at surveillance colonoscopy.

The model

The results of the MISCAN-COLON model are generated by micro-simulation of individuals in whom adenomas and subsequent colorectal cancer may develop. Although the MISCAN-COLON model is originally designed for evaluation of population based screening in an asymptomatic population, it can also be used to simulate surveillance after polypectomy. The output of the model consists of the adenoma and cancer detection rates at initial and surveillance colonoscopy and the effect of initial and surveillance colonoscopy on cancer incidence and mortality.

Parameter values in the expert-opinion-based model (expert MISCAN-COLON model) as presented in Table 5.1 have been established during two meetings at the United States National Cancer Institute [Loeve 1998, Loeve 1999, Loeve 2000]. In this expert model, it is assumed that adenomas are either non-progressive and will never develop into cancer in a lifetime or progressive and are destined to develop into colorectal cancer. The average duration between incidence of a progressive adenoma and clinical diagnosis of cancer is assumed to be 20 years. The duration between adenoma incidence and preclinical colorectal cancer is assumed exponentially distributed with a mean of 16.4 years, while the duration of preclinical cancer is exponentially distributed with a mean of 3.6 years. It is assumed that polypectomy completely prevents growth of the polyp into cancer.

If all individuals have equal risk for adenomas, i.e., adenomas are randomly distributed over the population, the resulting adenoma multiplicity is Poisson distributed. However, autopsy studies show a larger than Poisson variation [Koretz 1993], probably because of variation in genetic and environmental factors. The model accounts for the heterogeneity in adenoma multiplicity by drawing a risk index for each individual. The individual adenoma incidence rate is equal to the individual risk index multiplied by the age-specific adenoma incidence rate. This risk index is drawn from a gamma distribution with mean 1 and a variance of 2, which is chosen to fit the multiplicity distribution of adenomas in autopsy studies [Diggle 1994]. The probability that a new adenoma is progressive is age-dependent but does not depend on the individual risk index. The age-specific adenoma incidence and the probability that an adenoma is progressive is chosen to fit observed US cancer incidence in 1978 before the introduction of screening [National

Table 5.1 Main assumptions in the expert MISCAN-COLON model, established in expert meetings at the National Cancer Institute in 1996 and 1997.

Parameter	Value	Based on
Adenoma incidence	Age dependent: 40-49 yrs: 0.9% per yr 50-59 yrs: 1.9% per yr 60-69 yrs: 3.3% per yr 70-79 yrs: 2.6% per yr	Adenoma prevalence in autopsy and colonoscopy studies of 15% in age group 50-59 to 33% in age group 70+ [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993], cancer incidence in SEER registry in 1978 [National Cancer Institute 2001]
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2	Multiplicity distribution of adenomas in autopsy studies [Koretz 1993]
Duration distributions in preclinical stages	Exponential	Expert opinion, other cancer models [Walter 1983, Gyrd-Hansen 1997, Launoy 1997]
Mean duration of non-progressive adenomas	Lifelong	Expert opinion
Mean duration of progressive adenomas	16.4 yrs	Expert opinion
Mean duration of preclinical cancer	3.6 yrs	Cancer detection rate at first screening and background cancer incidence in FOBT trials [Hardcastle 1989, Kronborg 1989]
Probability to develop cancer from removed adenoma	0%	Expert opinion
Sensitivity of diagnostic and surveillance colonoscopy for adenomas	≤5mm: 80% 6-9mm: 85% 10+mm: 95%	Back-to-back colonoscopy studies [Hixson 1991, Rex 1997b, Rex 1997c]
Sensitivity of diagnostic and surveillance colonoscopy for cancer	95%	Back-to-back colonoscopy studies [Hixson 1991, Rex 1997b, Rex 1997c]

Cancer Institute 2001] and prevalence of adenomas in autopsy and colonoscopy studies [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993].

The participants in the National Polyp Study had adenomas diagnosed and removed. The MISCAN-COLON model is adapted to this situation by applying a

fictitious screening test to the general population to select individuals with adenomas detected at diagnostic colonoscopy. These individuals constituted the simulated trial population. Like in the National Polyp Study, simulated individuals with colorectal cancer diagnosed at the diagnostic colonoscopy were excluded from the trial population. The sensitivity of the fictitious screening test was adjusted to reproduce the age distribution, the distribution of adenomas over the distal and proximal colon, and the size and multiplicity-distribution of adenomas at initial polypectomy in the National Polyp Study.

In the National Polyp Study, incomplete surveillance colonoscopies (%) were followed by repeat colonoscopy. Therefore, we define a surveillance examination as a series of one or more colonoscopies in a short time period of which at least one reaches the cecum and the examination is considered to be of high confidence. The reach of a surveillance examination is assumed to be 100%, i.e., the complete bowel is visualized. The reach of the initial colonoscopy is also assumed to be 100% because patients with incomplete initial colonoscopies were excluded from the study. Sensitivity of the initial colonoscopy and the surveillance examinations is based on tandem studies of colonoscopy and increases from 80% for adenomas ≤5mm to 95% for preclinical cancer [Hixson 1991, Rex 1997b, Rex 1997c]. The simulated population of 5 independent simulations of 30,000 each (5*30,000=150,000) was designed to be approximately 100 times as large as the observed National Polyp Study cohort of 1,418 patients in minimize chance variation in the simulation results. The National Polyp Study surveillance schema and the observed compliance rates per arm and round are applied to the simulated trial population.

Analysis

Outcomes of the model are the simulated number of cancers during the trial and the simulated number of surveillance examinations at which adenomas are detected. The model further differentiates between cancers that are detected by a surveillance examination and those that are interval detected. These cancers are further subdivided into those originating from adenomas or preclinical cancers missed at initial colonoscopy, and those in newly developed, fast-progressing lesions.

The observed cancer and adenoma incidence rates in the trial were compared with the rates as simulated by the MISCAN-COLON model based on expert opinion. In case of discrepancies between observed and simulated results, we varied a few pivotal assumptions in order to search for models that are consistent with observed results. Parameters that were varied are the adenoma incidence in the trial population, the duration distribution of progressive adenomas, the spontaneous regression rates of non-progressive adenomas, and the sensitivity of colonoscopy.

The goodness of fit of each set of model assumptions is evaluated by the deviance, which compares five outcomes of the model with the observed National Polyp Study results. The results that are included in the deviance are the number of surveillance detected (asymptomatic) cancers (observed in the National Polyp Study: 5), the number of interval cancers (observed: 0), the number of surveillance examinations with adenomas in Arm A at the first surveillance examination (observed: 150 in 545 examinations), in Arm A at the 2nd surveillance examination (observed: 73 in 338 examinations) and in Arm B at

the first surveillance examination (observed: 137 in 428 examinations). The deviance is defined as

$$\sum_{i=1}^{5} 2 \cdot (k_i (\log p_i - \log \lambda_i) + (n_i - k_i) \cdot (\log(1 - p_i) - \log(1 - \lambda_i)))$$

where k_i is the observed number of occurrences for outcome i, n_i is the observed number of participants for the cancer results and the number of examinations for the adenoma results, $p_i=k_i/n_i$ is the observed rate, and λ_i is the simulated rate. A low deviance indicates a good fit with the National Polyp Study data. If the deviance is higher than 11.07, the simulated results are significantly different from the observed results in the National Polyp Study.

Results

MISCAN-COLON model based on expert opinion

Table 5.2 shows that the MISCAN-COLON model based on expert opinion simulated a

Table 5.2 Characteristics at initial polypectomy of all patients and their adenomatous polyps included in the National Polyp Study, as observed in the National Polyp Study and as simulated in the expert MISCAN-COLON model (n=1418).

Characteristic	Observed	Simulated
Age		
<50	13%	11%
50-59	28%	27%
60-69	39%	40%
70-79	18%	20%
80+	2%	3%
*Adenoma size**		
≤5mm	27%	27%
6-9mm	18%	17%
≥10mm	55%	56%
*No. of adenomas**		
1	57%	61%
2	22%	23%
≥3	20%	16%
*Site of largest adenoma**		
Distal colon	64%	61%
Proximal colon	36%	39%

* Forty-four patients with polyps classified as adenomas by the local pathologist were classified as non-adenomas by the review pathologists and were excluded from the National Polyp Study cohort simulated in this modeling study (n=1374).

cohort that successfully reproduced the characteristics at initial polypectomy of the National Polyp Study population. However, this expert MISCAN-COLON model simulates a cancer incidence during the surveillance period of 1.5 per 1000 person-years which is more than twice as high as the observed 0.6 (95% confidence interval 0.2-1.4), while it simulates a 18% adenoma detection rate at surveillance examinations which is considerably lower than the observed 27% (95% confidence interval, 25%-30%), see model A in Table 5.3. Of the simulated cancer incidence in the first six years after initial polypectomy, 61% is caused by cancers developed from new progressive adenomas, 22% is caused by missed adenomas that progressed into cancer and 18% is from preclinical cancers missed at initial colonoscopy. Of the simulated cancers, 40% is found at surveillance colonoscopy, and 60% are diagnosed because of symptoms, while in the National Polyp Study all 5 incident cancers were detected at surveillance. The overall goodness of fit of the expert model is poor, mainly caused by the poor fit of adenoma detection rates.

Natural history assumptions to better explain the observed rates

Higher model-simulated adenoma detection rates than in the expert MISCAN-COLON model can be achieved with a lower sensitivity of colonoscopy for adenomas or a higher adenoma incidence.

Low sensitivity for adenomas. The sensitivity for adenomas has to be extremely low in order to simulate the observed adenoma detection rates in the National Polyp Study, which conflicts with the low observed cancer incidence (model B in Table 5.3).

Higher adenoma incidence. The simulated adenoma detection rates are more in agreement with the observations when the adenoma incidence rate in the patients referred for colonoscopy is doubled (model C in Table 5.3). The resulting adenoma prevalence is not in agreement anymore with the adenoma prevalence in the unscreened general population which is about 33% in the 70+ age category [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993, Levin 1999]. However, the National Polyp Study cohort is a selected population with an adenoma incidence that may be higher than in the general population. A serious problem is that increasing the adenoma incidence also increases the risk for cancers, thus further increasing the already too high simulated cancer incidence (from 1.5 to 2.4 per 1000 person years compared to 0.6 observed). This could theoretically be resolved by restricting the increase in incidence to non-progressive adenomas. However, this would make the cancer risk in patients with multiple adenomas similar to the cancer risk in patients with only one adenoma, which is not consistent with published data that show that adenoma multiplicity is a risk factor for colorectal cancer [Lotfi 1986, Bertario 1999]. Therefore, assuming a higher adenoma incidence that is associated with a higher adenoma prevalence has to be rejected.

Higher adenoma incidence combined with regression. The high adenoma detection rates in the National Polyp Study can also be explained by assuming high adenoma incidence compensated by spontaneous regression of (non-progressive) adenomas. If spontaneous regression occurs regularly, adenoma incidence can be high while adenoma prevalence agrees with observed prevalence, even in older age groups where adenoma prevalence and multiplicity hardly increase according to autopsy and colonoscopy studies.

Table 5.3 Cancer incidence rate and proportion of surveillance examinations with adenomas as observed in the National Polyp Study population and as simulated with the expert MISCAN-COLON model and several model variants.

	Cancer rate per 1000 person years			Proportion of surveillance examinations with adenomas				
	Surveillance detected	Interval detected	All	Arm A, year 1	Arm A, year 3	Arm B, year 3	All	Deviance
Observed	**0.6**	**0.0**	**0.6***	**0.28**	**0.22**	**0.32**	**0.27****	
A. Expert MISCAN-COLON assumptions	0.6	0.9	1.5	0.17	0.13	0.25	0.18	84
Assumptions intended to raise the adenoma detection rate								
B. Low adenoma sensitivity (60%)	1.3	1.7	2.9	0.28	0.19	0.31	0.27	32
C. High adenoma incidence	1.0	1.4	2.4	0.26	0.21	0.36	0.28	28
D. High adenoma incidence and spontaneous regression	0.5	0.7	1.1	0.21	0.25	0.34	0.26	24
Assumptions intended to reduce the cancer incidence rate								
E. No fast-growing adenomas (constant duration of 20 yr)	0.3	0.3	0.6	0.16	0.11	0.23	0.17	104
F. High cancer sensitivity (100%)	0.5	0.7	1.2	0.17	0.12	0.24	0.18	83
Assumptions intended to fit both the cancer incidence and adenoma detection rate								
G. No fast-growing adenomas, high adenoma incidence and spontaneous regression	0.2	0.2	0.4	0.21	0.26	0.35	0.27	27
H. High cancer sensitivity, high adenoma incidence and spontaneous regression	0.4	0.6	1.0	0.22	0.25	0.34	0.26	23

* 95% Confidence interval 0.2-1.4

** 95% Confidence interval 0.25-0.30

Although it is generally assumed that adenomas grow into cancer or remain in the colon until death, spontaneous regression or washout of adenomas has been reported [Cole 1961, Knoernschild 1963, Hoff 1986, Giardiello 1993]. In the observational study of Knoernschild, the mucosa near asymptomatic benign polyps was tattooed in 257 patients. After follow-up of 3 to 5 years, the polyp had completely disappeared in 18% of the patients. Table 5.3 shows the results of model D in which non-progressive adenomas disappear on average after 5 years with an exponentially distributed duration. The adenoma incidence is three to five times higher than in the expert MISCAN-COLON model. Between the ages 55 years and 84 years the incidence is approximately 10% per

year with a peak in age group 70-74 years of 16% per year. This model variant results in adenoma detection rates that are more in agreement with the National Polyp Study observations. Because in this model most individuals will develop adenomas at some time during their life, the colorectal cancer risk in individuals with adenomas is less increased than in the expert MISCAN-COLON model. This explains why the simulated colorectal cancer incidence is lower than in the expert MISCAN-COLON and not significantly different from the observed colorectal cancer incidence (model D in Table 5.3).

In summary, a high adenoma incidence combined with spontaneous regression of adenomas is the only explanation of the observed adenoma detection rate that does not increase simulated cancer incidence and even decreases the simulated cancer incidence. The deviances of models B, C, and D are all lower than the deviance of the expert MISCAN-COLON model, which indicates that models B, C, and D are more in agreement with the National Polyp Study results. The simulated results of model B and C are still significantly different from the observed results ($P<0.05$), mainly due to the difference in interval-detected cancers. The simulated results of model D are significantly different from the observed results ($P<0.05$), due to the difference in interval-detected cancers and the simulated adenoma detection rate in Arm A, year 1.

To decrease the simulated cancer incidence further, we explored two possibilities for lowering the cancer incidence: no fast-growing progressive adenomas, and a high sensitivity of colonoscopy for cancer.

No fast-growing adenomas. In the expert MISCAN-COLON model, approximately 30% of the progressive adenomas will develop into cancer within six years, due to the exponentially distributed duration of 20 years on average. With fewer fast-growing progressive adenomas than assumed in the expert MISCAN-COLON model, cancers from new polyps will not surface in the first years after polypectomy and thus the incidence will remain low. As an example, model E in Table 5.3 is a model in which adenomas do not develop into cancer within the trial period, i.e., there are no fast-growing (within six years) progressive adenomas. Under these assumptions, none of the incident cancers in the first six years after polypectomy are newly developed, 74% develop from cancers missed at initial colonoscopy and 26% develop from adenomas missed at initial colonoscopy. The percentage of cancers developing from missed adenomas is small, because most missed adenomas are small and take more than six years to develop. In this simulation, 51% of the cancers are diagnosed at surveillance examinations, compared to 39% in the expert model. The simulated cancer incidence rate decreases from 1.5 to 0.6 per 1000 years, which is equal to the observed rate.

Higher sensitivity for cancer. The assumed sensitivity of colonoscopy for cancer is 95% in the expert model, based on a retrospective study of colonoscopic sensitivity for cancer [Rex 1997c]. However, in the NPS study sigmoidoscopy or barium enema was performed as the reason for referral for colonoscopy in 25% and 44% of the patients respectively [Winawer 1992] and often additional colonoscopies were performed to "resolve" cases, which gives extra opportunities to detect cancer in these patients. Raising the sensitivity for preclinical cancer in the MISCAN-COLON model from 95% to 100%

reduces the incidence from missed cancers. But because missed cancers cause only 18% of the cancer cases in the expert model, the decrease in cancer incidence is modest, from 1.5 to 1.2 per 1000 years (model F in Table 5.3).

Neither of these two assumptions that increase the cancer incidence in the study period affect the simulated adenoma detection rates, which remains too low. Because the deviance largely depends on the adenoma detection rates, the deviances of model E and F are comparable or higher than the expert MISCAN-COLON model (model A).

Table 5.3 shows the results of the MISCAN-COLON model with high adenoma incidence and spontaneous adenoma regression, combined with no fast-growing progressive adenomas (model G), and combined with 100% colonoscopic sensitivity for cancer (model H). The simulated cancer incidence in model G is more than 60% reduced compared to model F, while the simulated cancer incidence in model H is only slightly reduced compared to model F. In Model D the simulated cancer incidence is higher than observed, but not significantly different. If that model is modified with the assumption of no fast growing adenomas (model G), the simulated cancer incidence is lower than observed, but again not significantly different. Thus, models that include the assumption of development and regression of adenomas and in which the percentage of the progressive adenomas that will develop into cancer within six years is between 0% and 30% are consistent with the observed cancer incidence. The deviances of model G and H are comparable with the deviance of model D.

Discussion

The assumptions of the expert MISCAN-COLON model were developed in collaboration with the National Cancer Institute, United States, in meetings of a group of colorectal cancer experts [Loeve 1999]. In order to clarify the natural history of the adenoma-carcinoma sequence, a few pivotal natural history assumptions made by this group were modified to determine which natural history assumptions best fit the National Polyp Study observed data. The expert MISCAN-COLON model predicted a higher cancer incidence and lower adenoma detection rates than observed in the National Polyp Study. In order to have the highest concordance between the model results and the National Polyp Study results, a new factor had to be introduced, i.e., adenoma regression.

High adenoma incidence combined with regression accounted for the high percentage of patients with adenomas at surveillance, without losing its consistency with adenoma prevalence data from autopsy studies and without increasing the colorectal cancer incidence during the study. The high incidence is supported by a study of repeat colonoscopy that estimated that the 1-year adenoma incidence rate is 11% [Bensen 1999]. The assumption that adenomas spontaneously regress is supported by previous findings in short-term studies that adenomas may regress in size [Hoff 1986, Hofstad 1996]. A recent study of celecoxib in patients with familial adenomatous polyposis reported adenoma regression in the control group. In this study, a tattoo was placed at baseline endoscopy near a small area with a high density of polyps. Repeat endoscopy was performed six months later and the number of polyps at the tattooed area in the placebo group was 4.5%

less than at baseline endoscopy [Steinbach 2000]. The Telemark study recently reported that adenoma prevalence in patients who had undergone sigmoidoscopy 13 years before was not significantly lower than in the patient without previous sigmoidoscopy. The authors mention adenoma regression as one of the possible explanations [Thiis-Evensen 2001].

The cost-effectiveness of repeat sigmoidoscopy or colonoscopy colorectal cancer screening in the general population has been studied using models [Frazier 2000, Khandker 2000, Sonnenberg 2000]. None of these included the assumption that adenomas regress and adenoma incidence is accordingly high. High adenoma incidence combined with regression makes adenoma detection as a strategy for colorectal cancer prevention less favorable, because more adenomas will develop in the population after polypectomy. Furthermore, it is likely that more individuals will develop at least one adenoma. Thus, in repeat screening rounds, many adenomas will be detected in those without previous adenomas. There is less difference in risk level between individuals with and without adenomas, making surveillance of adenoma patients less effective. Also, many adenomas will be detected at surveillance in individuals with adenomas detected, as observed in the National Polyp Study. This increases the financial and quality of life costs expected of frequent surveillance and (endoscopic) screening.

The National Polyp Study provided the opportunity to examine the dynamics of the natural history of the adenoma-carcinoma sequence. The outcome suggests that the adenoma-carcinoma sequence is a dynamic process of formation and regression of adenomas. This has negative consequences for the effects and costs expected from endoscopic colorectal cancer screening and surveillance of adenoma patients.

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