REPORTS

Induced Abortion and Risk for Breast Cancer: Reporting (Recall) Bias in a Dutch Case–Control Study

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Background: In general, no association has been found between spontaneous abortion (naturally occurring termination of a pregnancy) and the risk for breast cancer. With respect to induced abortion (termination of a pregnancy by artificial means), the results have been more inconclusive. A positive association was found in five studies, no association was found in six studies, and a negative association was found in the only cohort study. It is thought that part of the inconsistency of the reported results may be attributable to reporting (recall) bias, since all but two studies on induced abortion used the case–control design and were based only on information obtained from study subjects. In comparison with breast cancer case patients, healthy control subjects may be more reluctant to report on a controversial, emotionally charged subject such as induced abortion. Thus, differential underreporting may be a cause of spurious associations in case–control studies. *Purpose:* Our goal was threefold: 1) to evaluate the relationship between a history of induced or spontaneous abortion and the risk for breast cancer in a Dutch population-based, case–control study; 2) to examine reporting bias by comparing risks between two geographic areas (i.e., western regions and southeastern regions in The Netherlands that differ in prevalence of and attitudes toward induced abortion); and 3) to compare reporting bias in data on induced abortion with reporting bias in data on oral contraceptive use. *Methods:* Data analyzed in this study were obtained from 918 women (20-54 years of age at diagnosis) who were diagnosed with invasive breast cancer during the period from 1986 through 1989 and had been initially enrolled in a population-based, case–control study investigating oral contraceptive use and breast cancer risk. The women resided in one of four geographic areas that were covered by Regional Cancer Registries: two western regions (Amsterdam and West) and two southeastern regions (East and Eindhoven). Each case patient was pair-matched, on the basis of age (within 1 year) and region, with a control subject who was randomly selected from municipal registries that fully covered the Dutch population. Both the case patients and the control subjects were interviewed at home by the same trained interviewer, who used a structured questionnaire. Reporting bias was examined indirectly by comparing risks between the western and the southeastern regions of the country, which differ in the prevalence of and attitude toward induced abortion. Multivariate conditional logistic regression methods for individually matched case–control studies were used to estimate relative risks (RRs). Reported *P* values are two-sided. *Results and Conclusion:* Among parous women, a history of induced abortion was associated with a 90% increased risk for breast cancer (adjusted RR = 1.9; 95% confidence interval [CI] = 1.1-3.2). Among nulliparous women, no association between induced abortion and breast cancer was found. Neither among parous women nor among nulliparous women was a history of spontaneous abortion related to the risk for breast cancer. The association between induced abortion and breast cancer was stronger in the southeastern regions of the country, which have a predominantly Roman Catholic population, than in the western regions (adjusted RR = 14.6 [95% CI = 1.8-120.0] versus adjusted RR = 1.3 [95% CI = 0.7-2.6], respectively; test of difference between regions, $P = .017$), suggesting reporting bias. Support for reporting bias as an explanation for the regional differences was also found in data supplied by both study subjects and their physicians on the use of oral contraceptives. In comparison with physicians, control subjects in the southeastern regions underreported the duration of their oral contraceptive use by 6.3 months more than control subjects in the western regions ($P = .007$). *Implication*: Reporting bias is a real problem in case–control studies of induced abortion and breast cancer risk if these studies are based on information from study subjects only. More quantitative assessment of this bias in future studies is essential. [J Natl Cancer Inst 1996; 88:1759-64]

The question of whether induced abortion increases the risk for breast cancer, which was first put forth in 1981 by Pike et al. (*1*), has received renewed attention with the 1994 report by Daling et al. (*2*). Daling et al. found that a history of induced abortion was associated with a 50% increase in breast cancer risk among women who had been pregnant at least once.

Interest in this association is based on the high level of breast cell proliferation

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observed during the first trimester of a pregnancy, which is followed by cell differentiation during the second and third trimesters. Russo and Russo (*3*) have hypothesized that a pregnancy interrupted by abortion increases the risk for breast cancer because breast cells may be left undifferentiated and thus more prone to oncogenic influences. This effect may be even stronger when the pregnancy is interrupted at the end of the first trimester (*2*) or when it is not preceded by a full-term pregnancy (*1*). Sixteen of the studies (*1,2,4-17*) that examined the association between abortion and the risk for breast cancer made a distinction between induced abortion (deliberate procedure to remove or expel an embryo or a fetus before it is viable outside the uterus) and spontaneous abortion (spontaneously occurring natural preterm termination of pregnancy). Such a distinction seems to be important, since women with spontaneous abortions may differ from women with normal pregnancies interrupted by induced abortions. For instance, hypersecretion of luteinizing hormone in the follicular phase may be associated with the risk for spontaneous abortion (*18*). Also, the levels of progesterone, human chorionic gonadotropin, and estradiol during early pregnancy are reduced in women having a spontaneous abortion (*19*). In general, no association has been found between spontaneous abortions and the risk for breast cancer (*1,2,4,5,7-17*), although a positive association between spontaneous abortions before the first birth and breast cancer risk was reported in one follow-up study (*6*). With respect to induced abortions, the results have been more inconclusive. A positive association was found in five studies (*1,2,7,10,15*), no association was seen in six studies (*5,8,11,12,14,17*), and a negative association was observed in the only cohort study (*9*). By studying the association among parous and nulliparous women separately, the issue was still not clarified.

Part of the inconsistency of the reported results may be attributable to misclassification bias, since all but two studies (*9,10*) of induced abortion used the case–control design and were based on information obtained from study subjects only. Compared with breast cancer patients, healthy control subjects may be more reluctant to report on a controversial, emotionally charged subject such as induced abortion. Thus, differential underreporting may cause spurious associations in case–control studies.

We evaluated the relationship between a history of induced or spontaneous abortion and the risk for breast cancer in a Dutch case–control study. This study provides a unique opportunity to examine reporting (recall) bias (arising when individuals with a particular adverse health outcome remember and report their previous exposure experience differently from those who are not similarly affected) (*20*) by comparing risks between two geographic areas that differ in prevalence of and attitude toward induced abortion. Reporting bias in our data on induced abortion was compared with reporting bias in our data on oral contraceptive use, for which a "gold standard" (i.e., information from former and current prescribers of oral contraceptives) was available.

Subjects and Methods

Case patients and control subjects. This population-based, case–control study was conducted to investigate the relationship between oral contraceptive use and breast cancer risk. The methodology of the study was described in detail elsewhere (*21*). Briefly, 918 case patients (20-54 years of age at diagnosis) diagnosed with invasive breast cancer during the period from 1986 through 1989 were included in the study. They resided in one of four regions covered by population-based Regional Cancer Registries in The Netherlands. In the two western regions (Amsterdam and West), they were younger than 45 years of age; in the two southeastern regions (East and Eindhoven), they were younger than 55 years of age. Each patient was pair-matched, on the basis of age (within 1 year) and region, with a control subject who was randomly selected from municipal registries that fully cover the Dutch population. The response rates of case patients and control subjects were 60% and 72%, respectively. A small nonresponse study among case subjects suggested that the majority of nonresponders had not been informed of the study by their doctors and thus had not been able to consider participation. In The Netherlands, where patient populations treated by various specialists have similar socioeconomic distributions, this situation implies a smaller selection than the response rates suggest (*21*).

Interview. Each case patient and her matched control subject were interviewed in their homes by the same trained female interviewer. During the 1.5-hour interview, a structured questionnaire was used, as well as a calendar on which all major life events and the woman's reproductive history were recorded. First, the interviewer asked about the total number of pregnancies and the duration of each pregnancy, irrespective of outcome. Then, the case patient or control subject was asked to provide further details (i.e., outcome) about each successive pregnancy ending with a live birth. Next, the interviewer inquired specifically about whether the woman had had a history of an ectopic pregnancy, a spontaneous or induced abortion, or a stillbirth; this question was followed again by detailed questions about each of these events. Finally, the total number of pregnancies was checked. Information on oral contraceptive use was collected from the women and their former and/or current prescriber(s) (*21*). If a woman said she had never used oral contraceptives, this was confirmed with her current general practitioner.

Statistical analysis. Each control subject was assigned a date of pseudo-diagnosis, i.e., the date on which she was exactly as old as her matching case patient at diagnosis. The analysis was restricted to events that had occurred in the period before pseudo-diagnosis for the control subjects and diagnosis for the case patients. Multivariate conditional logistic regression methods for individually matched case–control studies were used to estimate relative risks (RRs) (*22*). RRs were estimated separately for parous and nulliparous women and were based on models that included the interaction term with nulliparity. An analysis restricted to parous pairs (n = 673) yielded comparable results. All P values reported were derived from two-sided tests of statistical significance.

Indirect evaluation of reporting bias. In The Netherlands, no complete abortion registry is available for the period of interest. However, reporting bias could be evaluated indirectly by a comparison of the study results between two areas, the western and southeastern parts of the country. Historically, the proportion of Roman Catholic women has been higher in the southeastern regions (63%) than in the western regions (28%), and the proportion without affiliation with any church is also known to differ markedly [southeastern versus western: 10% versus 32%, respectively, as of the 1970s, when most of the abortions in our study were reported (*23*)]. Induced abortion rates in the southeastern regions have always been lower than in the western regions [e.g., in 1985, there were four abortions per 1000 individuals per year in the southeastern regions compared with eight per 1000 per year in the western regions (*24*)]. These figures illustrate that the western regions take a more liberal position toward an induced abortion. If reporting bias plays a role, we would expect a higher RR estimate for the southeastern regions than for the western regions as a result of more underreporting by control subjects than by case patients in the former regions. While comparing the two areas, we excluded women aged 45-54 years, since women in this age category were enrolled in the southeastern regions only.

Results

In the group of 918 healthy control subjects, only 36 women (4%) reported having had an induced abortion. These abortions took place in the period from 1959 through 1987 (median, 1976). As

shown in Table 1, the proportion of women who had had induced abortion was highest in the western part of The Netherlands. Only two women reported two induced abortions each (data not shown). An induced abortion was reported more frequently by women with a higher education and by nulliparous women.

A spontaneous abortion was reported by 196 (21.4%) of the 918 case patients and 193 (21.0%) of the 918 control subjects. Twelve case patients and four control subjects reported an induced as well as a spontaneous abortion (data not shown).

In the overall study, induced abortion was associated with a 90% increased risk for breast cancer (adjusted RR = 1.9; 95% confidence interval [CI] = 1.1-3.2) among parous women (Table 2). The risk elevation was slightly higher for parous women who reported an induced abortion before their first full-term pregnancy (adjusted RR = 2.6; 95% CI = 1.0-6.8), but the numbers in this category were small. No marked differences were found according to age at first abortion or gestational length of the first aborted pregnancy. Among ever-pregnant women, these estimates were nearly the same. In nulliparous women, no association was found between induced abortion and risk for breast cancer.

A history of spontaneous abortion was not associated with risk of developing breast cancer (adjusted RR = 1.1 [95% CI = 0.9-1.5] in parous women; adjusted RR = 0.5 [95% CI = 0.2-1.2] in nulliparous women). The risk was roughly comparable for the subgroups described in Table 2, with the possible exception of those who had had a spontaneous abortion before first birth (adjusted RR = 1.4; 95% CI = 1.0-1.9).

We examined reporting bias by comparing two study areas, i.e., the western part and the southeastern part of the country, in which the impact of reporting bias was expected to be most pronounced. Among parous women with a history of induced abortion, the estimated RR for breast cancer was significantly higher in the southeastern regions (adjusted RR = 14.6; 95% CI = 1.8-120) than in the western regions (adjusted RR = 1.3; 95% CI = 0.7-2.6) (test for difference, P = .017; Table 3). With regard to spontaneous abortions, no difference was found between the RR estimates for the two areas (adjusted RR = 1.3 [95% CI = 0.9-1.9] for southeastern regions compared with adjusted RR = 1.1 [95% CI = 0.7-1.8] for western regions) (test for difference, P = .64) (data not shown).

Women who are reluctant to report induced abortions may also tend to slightly underreport their use of oral contraceptives. For oral contraceptive use, reporting bias could be directly evaluated, since we collected information on oral contraceptive use from both the women and their current or former prescribers (*21*). We took into account only the duration of oral contraceptive use within the period for which prescriber information was available (86% of life-time use of oral contraceptives). In comparison with the prescribers, control subjects in the southeastern regions underreported the duration of their oral contraceptive use by 6.3 (6.8 – 0.5 = 6.3) months more than control subjects in the western regions (P = .007; Table 4). This underreporting of duration of oral contraceptive use in the southeastern regions compared with the western regions supports our assumption that underreporting of induced abortions is the most likely explanation for the regional differences in the association between induced abortion and breast cancer risk.

Finally, we investigated potential regional differences in the association between reported durations of oral contraceptive use

Table 1. Characteristics of case patients with breast cancer and population-based control subjects (n = 918 pairs) by history of induced abortion

Characteristic	No. of case patients/No. of control subjects	
	Ever had induced abortion	Never had induced abortion
Age, y		
≤35	5/7	127/125
36-40	20/17	199/202
41-45	23/9	297/311
46-54	8/3	239/244
Area		
Western	34/29	377/375
Southeastern	22/7	485/507
Education		
Low	21/8	437/411
Medium	25/15	309/363
High	10/13	116/108
Parity		
Yes	43/26	716/775
No	13/10	146/107
Age at first full-term pregnancy, y		
≤21	12/8	103/144
22-24	9/6	215/244
25-26	9/4	170/172
27-29	5/4	146/138
≥30	8/4	82/77
Nulliparous	13/10	146/107
No. of full-term pregnancies		
1	10/4	114/119
2	25/17	406/428
3	5/4	151/170
≥4	3/1	45/58
Nulliparous	13/10	146/107
Family history of breast cancer		
None	33/26	567/677
First-degree relative	8/2	111/55
Second-degree relative	15/8	184/150
Use of oral contraceptives, y		
0	4/2	130/134
<4	16/14	229/255
4-7	13/7	228/236
8-11	13/10	149/152
≥12	10/3	126/105
Total	56/36	862/882

Table 2. Relative risk (RR) of developing breast cancer in relation to prior induced abortion in 918 case–control pairs

	No. of case patients/ No. of control subjects	Unadjusted RR (95% confidence interval)	Adjusted* RR (95% confidence interval)
	Parous women (759 case patients and 801 control subjects)		
Induced abortion			
Never	716/775	1.0 (referent)	1.0 (referent)
Ever	43/26	1.8 (1.1-3.0)	1.9 (1.1-3.2)
Timing of first induced abortion			
Before first birth	13/7	2.1 (0.8-5.3)	2.6 (1.0-6.8)
After first birth	30/19	1.7 (1.0-3.1)	1.7 (0.9-3.1)
Age at first induced abortion, y			
≤30	23/16	1.5 (0.8-3.0)	1.8 (0.9-3.6)
>30	20/10	2.3 (1.1-4.9)	2.0 (0.9-4.5)
Gestational length of first aborted pregnancy, wk			
≤8	25/14	2.0 (1.0-3.8)	2.1 (1.1-4.2)
>8	18/12	1.6 (0.8-3.4)	1.6 (0.8-3 5)
	Nulliparous women (159 case patients and 117 control subjects)		
Induced abortion			
Never	146/107	1.0 (referent)	1.0 (referent)
Ever	13/10	0.9 (0.4-2.2)	0.9 (0.4-2.3)

*Adjusted for spontaneous abortion, age at first full-term pregnancy, number of full-term pregnancies, weeks of breastfeeding, family history of breast cancer, and use of injectable contraceptives.

and risk for breast cancer. Small regional differences in the expected direction (higher risk in southeastern area) seemed to be present in data reported by study subjects (≤45 years) only; the association seemed somewhat stronger in the southeastern regions than in the western regions, although the difference was not statistically significant (for ≥12 years of oral contraceptive use as compared with <4 years of oral contraceptive use: RR = 1.3 versus RR = 0.9 for the southeastern and western regions, respectively; test of interaction: $P = .158$). When information from study subjects and their prescribers was combined (*21*), these regional differences between oral contraceptive use and breast cancer risk were no longer present (RR = 0.9 versus RR = 1.1, respectively; test of interaction: $P = .433$).

Discussion

In this case–control study, we found evidence that the estimated 90% increased risk for breast cancer after induced abortion was largely attributable to underreporting of abortion by healthy control subjects. Within the more liberal western regions of The Netherlands, the association was still in the positive direction, but it was weaker and no longer statistically significant (adjusted RR = 1.3; 95% CI = 0.7-2.6). Since even this estimate may not be completely free of reporting bias, our study does not support an appreciably increased risk for breast cancer after an induced abortion. A spontaneous abortion was not found to be related to breast cancer risk, although this estimate may have been biased toward the null as a result of underreporting by both case patients and control subjects (*25*).

In The Netherlands, induced abortion was not legalized until 1984. Thus, 98% of the reported induced abortions in this study took place before legalization. However, from 1967 onward, induced abortions were allowed in specific hospitals. Current induced abortion rates in The Netherlands are still very low (six abortions per 1000 individuals per year, compared with those in the United States in which there are 30 abortions per 1000 individuals per year) (*26*). This lower rate in The Netherlands is attributable to the wide availability of oral contraceptives and the "morning-after" pill, open sex education, and the relatively high proportion of educated women within the traditionally homogeneous population.

Few studies have examined the validity of self-reported information about abortions. Jones and Forrest (*27*) studied the issue in a representative sample of U.S. women (15-44 years of age) participating in the National Survey of Family Growth. They compared interview as well as questionnaire data with national abortion data. They estimated that no more than 60% of

Table 3. Relative risk (RR) of developing breast cancer at ages 20-45 years in relation to prior induced abortion in parous women in the western and southeastern regions

	Western regions (315 case patients and 348 control subjects)			Southeastern regions (225 case patients and 230 control subjects)		
	No. of case patients/No. of control subjects	Unadjusted RR	Adjusted* RR (95% confidence interval)	No. of case patients/No. of control subjects	Unadjusted RR	Adjusted* RR (95% confidence interval)
Induced abortion						
Never	292/326	1.0	1.0 (referent)	213/229	1.0	1.0 (referent)
Ever	23/22	1.2	1.3 (0.7-2.6)	12/1	12.3	14.6 (1.8-120)
Test of difference between regions			$P = .017$†			

*Adjusted RR for spontaneous or induced abortion, age at first full-term pregnancy, number of full-term pregnancies, weeks of breastfeeding, family history of breast cancer, and use of injectable contraceptives.
†Two-sided.

Table 4. Regional differences in duration of use of oral contraceptives (OCs) reported by women (≤45 years of age) minus duration of use according to prescribers*

Region	No. of case patients	Difference in duration of OC use in months, mean ± SEM†	No. of control subjects	Difference in duration of OC use in months, mean ± SEM†	*t* test‡
Western	246	−3.1 ± 1.5	231	−0.5 ± 1.5	$P = .235$
Southeastern	169	−2.3 ± 1.6	153	−6.8 ± 1.8	$P = .061$
	$P = .735$		$P = .007$		

*For each woman, a period was defined for which prescriber information was available [generally the period between the first starting date and the last stopping date according to her prescriber(s)]. Within this defined period, the difference of the duration of OC use according to the woman and her prescriber(s) was calculated; please note that the negative sign of the difference in duration of OC use in months results from not taking into account half of the random variation of the corresponding starting and stopping dates according to the woman (i.e., an earlier reported starting date or a later stopping date). By this method, we excluded the period of time that a prescriber could not provide OC information.

†Mean (± standard error of the mean [SEM]) difference = $\frac{\sum_{i=1}^{N}(x_{wi} - x_{pi})}{N}$, where x_{wi} is duration of OC use according to woman i and x_{pi} is duration of OC use according to her prescriber(s).

‡P value obtained by use of Student's t test (two-sided).

all induced abortions were reported. Underreporting was more pronounced in data collected by means of in-person interviews than in data collected by means of a written questionnaire. In addition, the underreporting was more pronounced if information concerning the total number of induced abortions experienced was obtained before a detailed pregnancy history was obtained. Previous reports on breast cancer risk after an induced abortion do not provide much detail about the actual questions that were asked. In our study, we did not raise the issue of pregnancy outcome before collecting information about the total number of pregnancies and their durations (*see* "Subjects and Methods" section).

Lindefors-Harris et al. (*28*) were the first to show that differential misclassification bias is a potential problem in case–control studies eliciting information on induced abortions. They compared information about induced abortions reported by patients with breast cancer and control subjects with data from an abortion registry that was used as the gold standard. Control subjects underreported their abortion history more frequently than case patients. This result is indicative of reporting bias, but the study is not fully conclusive because the registry was not complete. Daling et al. (*2*) concluded that reporting bias in their positive study on induced abortion and breast cancer was unlikely, since they found no association between induced abortion and cervical cancer in the same population. Although this finding argues against reporting bias, patients with cervical cancer may differ from patients with breast cancer in reporting induced abortions, and, furthermore, the actual association between induced abortion and cervical cancer is not known. In a recent case–control study by Newcomb et al. (*17*), a stronger association between breast cancer and induced abortion was found for abortions performed in the United States before legalization than for abortions performed after legalization (RR = 1.4 versus 1.1). This suggestion of reporting bias is in line with our findings.

In conclusion, a reliable abortion registry seems to be essential when studying a sensitive issue such as induced abortion. Thus far, few case–control studies have properly examined the validity of the reported information concerning induced abortions. Our study shows that reporting bias is a real problem and that it deserves more quantitative assessment in case–control studies that are based on information from study subjects only.

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Notes

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Angiogenesis as a Predictor of Long-term Survival for Patients With Node-Negative Breast Cancer

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Background: **Angiogenesis (the formation of new blood vessels) is necessary for tumor growth and metastasis.** ***Purpose:*** **We investigated whether angiogenesis as measured by microvessel count (MVC) predicts clinical outcome in a series of patients with axillary lymph node-negative breast cancer who received no adjuvant therapy and who were followed for a long period of time. Our long-term goal is to identify those patients who may or may not need adjuvant chemotherapy.** ***Methods:*** **Pathologic archival material and clinical information were analyzed for 167 patients treated with mastectomy from 1941 through 1987; none received adjuvant treatment. The median follow-up time among living patients was 15.4 years (range, 2.6-35.8 years). Ninety-six (58%) patients had a tumor size of 2 cm or less, 52 (31%) had tumors of 2.1-3 cm, and 19 (11%) had tumors of larger than 3 cm. Paraffin-embedded tissue sections were stained for expression of CD34 antigen on microvessel-associated endothelial cells by use of a monoclonal anti-CD34 antibody. Vascularity was defined as the number of microvessels (average of the three highest counts) per high-power microscopic field (400× magnification) in the area of highest vascular density. A high vascular count was defined as 15 or more microvessels per field. Actuarial survival curves were calculated according to the Kaplan–Meier method and comparisons were made with the logrank test. The Cox proportional hazards model was used for multivariate analysis. All *P* values were based on two-sided testing.** ***Results:*** **The 20-year disease-free survival (DFS) for the 167 node-negative patients treated with mastectomy and no adjuvant therapy was 74.8% (95% confidence interval [CI] = 64.7%-82.0%). The 20-year DFS was 93.1% (95% CI = 79.9%-97.7%) if the MVC was low versus 68.9% (95% CI = 56.8%-78.0%) if the MVC was high (*P* = .018). This difference was maintained irrespective of tumor size: for tumor size of 2 cm or less (93.3% [95% CI = 75.3%-98.3%] versus 67.8% [95% CI = 50.1%-80.3%]) and for tumor size of larger than 2 cm (92.3% [95% CI = 56.6%-98.9%] versus 70.9% [95% CI = 54.6%-81.6%]). However, the likelihood of a high MVC was greater with large tumors (*P* = .05). The proportions of tumors with low and high MVC were 33% and 67%, respectively, if the tumor size was 2 cm or less, and 20% and 80%, respectively, if tumor size was larger than 2 cm. There was no significant difference in the 20-year DFS as a function of tumor grade (*P* = .2). After combining patients with tumors of nuclear grades 2 and 3 compared with those of nuclear grade 1, the 20-year DFS was 93.9% (95% CI = 77.2%-98.4%) for low MVC versus 66.9% (95% CI = 52.2%-78.0%) for high MVC (*P* = .02). In a multivariate analysis that included the variables tumor size, age, nuclear grade, estrogen receptor status, and MVC, only MVC appeared to be an independent prognostic indicator (*P* = .04).** ***Conclusions:*** **Angiogenesis as measured by MVC is a reliable independent prognostic marker of long-term survival in patients with node-negative breast cancer. The prognostic usefulness of this marker is maintained after more than 15 years of follow-up. A low MVC identifies a subgroup of patients with DFS of 92% or more, independent of tumor size or grade. [J Natl Cancer Inst 1996;88: 1764-9]**

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See "Notes" section following "References."