Marginal Structural Models as a Tool for Standardization

Tosiya Sato and Yutaka Matsuyama

Abstract: In this article, we show the general relation between standardization methods and marginal structural models. Standardization has been recognized as a method to control confounding and to estimate causal parameters of interest. Because standardization requires stratification by confounders, the sparse-data problem will occur when stratified by many confounders and one then might have an unstable estimator. A new class of causal models called marginal structural models has recently been proposed. In marginal structural models, the parameters are consistently estimated by the inverse-probability-of-treatment weighting method. Marginal structural models give a nonparametric standardization using the total group (exposed and unexposed) as the standard. In epidemiologic analysis, it is also important to know the change in the average risk of the exposed (or the unexposed) subgroup produced by exposure, which corresponds to the exposed (or the unexposed) group as the standard. We propose modifications of the weights in the marginal structural models, which give the nonparametric estimation of standardized parameters. With the proposed weights, we can use the marginal structural models as a useful tool for the nonparametric multivariate standardization.

Key Words: causal models, confounding, epidemiologic methods, standardization, weighted analysis

(*Epidemiology* 2003;14: 680–686)

Standardization methods have been used in epidemiology for a long time.[1,2] The related idea of calculating the expected number of deaths goes back to 18th century actuarial mathematicians.[3] Standardization methods are used to control confounding, and one can estimate causal parameters of interest through standardization.[4-7] Standardized estimators, such as the standardized mortality/morbidity ratio (SMR), are calculated by stratification on a set of confounding factors.

When the number of confounding factors used in stratification is increased, the data become sparse. In that case, estimated standardized parameters tend to be unstable. To alleviate this lack of stability, parametric model-based standardization methods have been proposed.[8,9] These methods depend heavily on the correct specification of the parametric model forms, which are usually unknown in epidemiologic applications.

Recently, Robins and colleagues[10,11] have proposed a new class of causal models called marginal structural models. Their weighted analysis gives an asymptotically unbiased estimate of the causal parameter of interest with the inverse of the conditional probability of receiving the subject's own exposure or treatment as a weight. As given in Appendix 1 by Robins et al.,[10] in a simple stratified point exposure analysis, their estimator is identical to the standardized estimator with the total group as the standard population. Hence, the marginal structural model is interpretable as a nonparametric multivariate standardization method.

In this article, we propose to use different sets of weights in the marginal structural models. The proposed approach gives the general standardization framework in the context of the marginal structural models.

Methods of Standardization

Suppose the data are stratified by combinations of multiple confounding factors or a propensity score.[5,12] Table 1 gives the data layout in the kth stratum. The second row (x_k, y_k) denotes pairs of the number of outcome events (eg, deaths) among the exposed and the unexposed. The last row (n, m_k) denotes pairs of the exposed and the unexposed subjects in the risk ratio estimation, or pairs of the exposed and the unexposed person-time denominators in the rate ratio estimation.

To illustrate standardization methods, we use an example of the effect of tamoxifen use (exposed: TAM = 1, unexposed: TAM = 0) on the recurrence of breast cancer (recurrence: RECUR = 1, no recurrence: RECUR = 0). Detailed multivariate person-time analysis is given in a later section. Table 2 shows the crude data and the data stratified by lymph node metastasis at surgery (positive: LYM = 1,

Submitted 26 August 2002; final version accepted 23 May 2003.
From the Department of Biostatistics, Kyoto University School of Public Health, Kyoto, Japan.
This study was supported in part by the 2000 Inamori Grant Program, the Inamori Foundation.
Correspondence: Tosiya Sato, Department of Biostatistics, Kyoto University School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: shun@pbh.med.kyoto-u.ac.jp.

1044-3983/03/1406-0680
DOI: 10.1097/01.EDE.0000081989.82616.7d

TABLE 1. Notation for the *k*th Stratum

	Exposed	Unexposed
Outcome Events	x_k	y_k
Denominator	n_k	m_k

negative: LYM = 0). No effect of tamoxifen was observed in the crude data (the crude risk ratio is 1.01). However, possible protective effects and effect-measure modification were observed in the stratified data (the stratum-specific risk ratios are 0.91 and 0.67, respectively).

When the target population of the study is the exposed group and one needs to summarize the overall effect of exposure in the ratio scale, the standardized mortality/morbidity ratio (SMR) is such a measure, which is given by:

$$SMR = \frac{\sum_k x_k}{\sum_k n_k \frac{y_k}{m_k}}.$$

The numerator of *SMR* can be interpreted as the number of deaths (or events) in the exposed group when the exposed group was actually exposed, which is identical to the observed number of deaths. In contrast, the denominator can be interpreted as the expected number of deaths in the exposed group if the exposed group had not been exposed.[4,6] Note that this expectation is not the null (no effect) expectation, which is given by $\Sigma_k n_k t_k/N_k$, where $t_k = x_k + y_k$ and $N_k = n_k + m_k$. It is instead the counterfactual number of deaths as if the exposed had not been exposed, because in the *k*th stratum we could substitute y_k/m_k for the counterfactual disease frequency in the exposed when confounding is removed by stratification.[6]

In the example in Table 2, *SMR* is calculated by:

$$SMR = \frac{368 + 96}{1215 \times \frac{253}{760} + 1334 \times \frac{171}{1592}}$$

$$= \frac{368 + 96}{404.5 + 143.3} = \frac{464}{547.8} = 0.85.$$

The *SMR* is interpreted as the proportionate change in risk (or rate) of the exposed group produced by exposure. In the calculation of *SMR*, the exposed group is used as the standard population. This is also known as the indirect standardization. Other choices of target population that are commonly used in epidemiologic studies are the unexposed group and the total group (combining the exposed and the unexposed groups).[13]

When the unexposed group is the target population and is chosen as the standard population, the standardized risk (or rate) ratio in the unexposed is given by:

$$SRR_U = \frac{\sum_k m_k \frac{x_k}{n_k}}{\sum_k y_k}.$$

This is known as the direct standardization. In our example, it is calculated as:

$$SRR_U = \frac{760 \times \frac{368}{1215} + 1592 \times \frac{96}{1334}}{253 + 171}$$

$$= \frac{230.2 + 114.6}{253 + 171} = \frac{344.8}{424} = 0.81.$$

TABLE 2. Crude and Stratified Count Data of the Tamoxifen Use and the Recurrence of Breast Cancer

	Crude Data		LYM = 1		LYM = 0	
	TAM = 1	TAM = 0	TAM = 1	TAM = 0	TAM = 1	TAM = 0
RECUR = 1	464	424	368	253	96	171
Total no.	2549	2352	1215	760	1334	1592
Risk ratio	1.01		0.91		0.67	

LYM = 1 (positive for lymph node metastasis at surgery), 0 (negative); TAM = 1 (exposed to tamoxifen), 0 (unexposed); RECUR = 1 (recurrence of breast cancer).

SRR_U is interpreted as the proportionate change in the risk (or rate) that would have occurred in the unexposed group had they been exposed.

When the total group (combining the exposed and the unexposed) is the target population, the standardized risk (or rate) ratio in the total group,

$$SRR_T = \frac{\sum_k N_k \frac{x_k}{n_k}}{\sum_k N_k \frac{y_k}{m_k}},$$

is calculated as:

$$SRR_T = \frac{1975 \times \frac{368}{1215} + 2926 \times \frac{96}{1334}}{1975 \times \frac{253}{760} + 2926 \times \frac{171}{1592}}$$

$$= \frac{598.2 + 210.6}{657.5 + 314.3} = \frac{808.8}{971.8} = 0.83$$

SRR_T is interpreted as the proportionate change in risk (or rate) in the total group under complete exposure and complete nonexposure.

The interpretations of these standardized parameters are still valid even when there is effect–measure modification. In other words, stratum specific ratios are heterogeneous.

Marginal Structural Models and Standardization

We explain the marginal structural models in the context of causal risk ratio estimation. Application to the estimation of other effect measures is straightforward.[10] In the estimation of the effect of a dichotomous exposure E (1: exposed, 0: unexposed) on a dichotomous outcome D (1: event occurred, 0: no event), we consider the contrast of the following potentially counterfactual probabilities:

$$P(D = 1|\text{set } E = 1) \text{ and } P(D = 1|\text{set } E = 0)$$

for the probability of $D = 1$ if everyone in the target population had been exposed ("set $E = 1$") and if everyone in the target population had not been exposed ("set $E = 0$").[2,7] Note that the counterfactual probability, $P(D = 1|\text{set } E = e)$, can be different from the observed probability, $P(D = 1|E = e)$, because the latter refers to a subset of population members with $E = e$, whereas the former refers to all population members.

In the marginal structural models, the marginal distribution of the counterfactual probabilities is modeled as:

$$\log P(D = 1|\text{set } E = e) = \alpha_0 + \alpha_1 e, \quad (1)$$

where $\exp(\alpha_1)$ is the causal risk ratio. The corresponding log-linear model for the observed probability can be written as:

$$\log P(D = 1|E = e) = \theta_0 + \theta_1 e, \quad (2)$$

where $\exp(\theta_1)$ is the crude risk ratio. This is an association model. Because this model is for the observed data, asymptotically unbiased estimates for the association parameters θ_0 and θ_1 are obtained through standard statistical software. However, the association parameter θ_1 will differ from the causal parameter α_1 except when exposure is unconfounded.

Robins et al.[10] have proposed a weighted analysis procedure for this association model, which in turn gives unbiased estimates of causal parameter α_1. First, we assume that we have no unmeasured confounders given data on measured confounders Z. Next, we assign a weight w_{Ti} to each subject i which is equal to the inverse of the conditional probability of receiving the subject's own exposure e_i conditional on the subject's confounder information z_i, $P(E|Z)$. With these weights, we perform the weighted analysis of the association model. Because the propensity score is defined as the conditional probability of receiving exposure, $P(E = 1|Z = z_i)$,[5] the weights for the exposed subjects are the inverse of $P(E = 1|Z = z_i)$ and those for the unexposed subjects the inverse of $P(E = 0|Z = z_i) = 1 - P(E = 1|Z = z_i)$. The resultant estimator is called the inverse probability of treatment weighted (IPTW) estimator.

To see the relation between the standardization with the total group as the standard and the marginal structural model, we write SRR_T as:

$$SRR_T = \frac{\sum_k N_k \frac{x_k}{n_k}}{\sum_k N_k \frac{y_k}{m_k}} = \frac{\sum_k x_k \left(\frac{n_k}{N_k}\right)^{-1}}{\sum_k y_k \left(\frac{m_k}{N_k}\right)^{-1}}.$$

In the simple stratified analysis, the conditional probability of receiving exposure for subjects in the kth stratum is n_k/N_k, and hence the conditional probability of receiving nonexposure is $1 - n_k/N_k = m_k/N_k$. It is obvious that the standardized risk ratio with the total group as the standard, SRR_T, is identical to the IPTW estimator in the marginal structural model (see Appendix 1).

Table 3 displays this process when we applied the IPTW method to the stratified data given in Table 2. Table 3

TABLE 3. Inverse Probability of Treatment Weights w_T, SMR Weights w_E, and Composition of Pseudopopulation

LYM	TAM	RECUR	Observed No.	P(E‖Z)	w_T	Pseudo No. Total	w_E	Pseudo No. Exposed
1	1	1	368	0.615	1.63	598.2	1	368
1	1	0	847	0.615	1.63	1376.8	1	847
1	0	1	253	0.385	2.60	657.5	1.60	404.5
1	0	0	507	0.385	2.60	1317.5	1.60	810.5
0	1	1	96	0.456	2.19	210.6	1	96
0	1	0	1238	0.456	2.19	2715.4	1	1238
0	0	1	171	0.544	1.84	314.3	0.84	143.3
0	0	0	1421	0.544	1.84	2611.7	0.84	1190.7

LYM = 1 (positive for lymph node metastasis at surgery), 0 (negative); TAM = 1 (exposed to tamoxifen), 0 (unexposed); RECUR = 1 (recurrence of breast cancer), 0 (no recurrence).

gives the observed number of women with each of the possible combinations of lymph node metastasis (LYM), tamoxifen use (TAM), and recurrence of breast cancer (RECUR) as well as the IPT weights $w_T = 1/P(E = e|Z = z)$. For example, $P(\text{TAM} = 1|\text{LYM} = 1)$ is calculated in the LYM = 1 stratum as the total number of tamoxifen-used (exposed) women (1215) divided by the total number of women (1975) which yields 0.615. Then, the IPT weights in the LYM = 1 stratum are 1.63 = 1/0.615 for the exposed women and 2.60 = 1/(1 − 0.615) = 1/0.385 for the unexposed women. The column "Pseudo No. Total" represents the number of women in the weighted pseudo-population for each combination of (LYM, TAM, RECUR). Table 4 displays the crude data from the pseudo-population created by the IPT weights. The crude risk ratio is 0.83, which is identical to the SRR_T.

We can interpret the marginal structural models associated with the IPTW estimator as a nonparametric multivariate extension of the standardization method with the total group as the standard.

Proposed Weights

Although the IPTW estimator is useful for estimating the population intervention effects, the standardization method with either the exposed group or the unexposed group as the standard is also useful in epidemiologic applications. We show that with the modified weights, we obtain the extensions of *SMR* or SRR_U in the marginal structural models. Similar to SRR_T, *SMR* can be rewritten as:

$$SMR = \frac{\sum_k x_k}{\sum_k n_k \frac{y_k}{m_k}} = \frac{\sum_k x_k \left(\frac{n_k}{N_k}\right)^{-1} \frac{n_k}{N_k}}{\sum_k y_k \left(\frac{m_k}{N_k}\right)^{-1} \frac{n_k}{N_k}}.$$

The weights implicitly used in *SMR* can be interpreted as the inverse of the conditional probability of receiving the subject's own exposure multiplied by the conditional probability of receiving exposure regardless of the subject's actual exposure status (see Appendix 1). This leads to a new weight for the *i*th subject:

$$w_{Ei} = \frac{P(E = 1|Z = z_i)}{P(E = e_i|Z = z_i)}. \quad (3)$$

We call this the SMR weight. In the SMR weight, the denominator works to control confounding in the same way as in the inverse probability of treatment weights; the numerator reweights the pseudo-population to give it the distribution of covariates in the target population (here, the exposed).

The weighted analysis of the association model (2) with new weights (3) gives unbiased estimates of the parameters in the following marginal structural model:

$$\log P(D = 1|\text{set}E = e, E = 1) = \beta_0 + \beta_1 e,$$

where "set $E = e$, $E = 1$" means what would have occurred in the exposed group had the exposed group taken the exposure e. The resultant estimator for $\exp(\theta_1)$, which is

TABLE 4. Crude Data From the Pseudopopulation Created by the Inverse Probability of Treatment Weights

	Exposed	Unexposed
Recurrence	808.8	971.8
No. of women	4901	4901
	Crude risk ratio = 0.83	

TABLE 5. Crude Data from the Pseudopopulation Created by the SMR Weights

	Exposed	Unexposed
Recurrence	464	547.8
No. of women	2549	2549
Crude risk ratio = 0.85		

consistent with causal parameter $\exp(\beta_1)$, has the interpretation as a nonparametric multivariate extension of the standardized mortality ratio. For the exposed subjects the weight w_{Ei} is always 1 and for the unexposed subjects it is the conditional exposure odds. Table 3 also displays the SMR weighting scheme. The SMR weight w_E in the LYM = 1 stratum is calculated as the total number of exposed women (1215) divided by the total number of unexposed women (760), which yields 1.60. The last column, "Pseudo No. Exposed," represents the number of women in the SMR-weighted pseudo-population. Table 5 displays the crude data from the pseudo-population created by the SMR weights. The crude risk ratio is 0.85, which is identical to *SMR*.

Parallel arguments give the extension of the standardization method with the unexposed group as the standard. The marginal structural model can be written as:

$$\log P(D = 1|\text{set}E = e, E = 0) = \gamma_0 + \gamma_1 e,$$

and we have unbiased estimates of (γ_0, γ_1) by the weighted analysis of the association model (2) with weights

$$w_{Ui} = \frac{P(E = 0|Z = z_i)}{P(E = e_i|Z = z_i)}. \quad (4)$$

In Table 6, a summary of different sets of weights is given when we use the logistic model

$$\text{logit } P(E = 1|Z = z_i) = \lambda' z_i$$

TABLE 6. Weights Used in Marginal Structural Models With Different Standard Populations When Propensity Scores are Estimated by the Logistic Model: logit $P(E = 1|Z = z_i) = \lambda' z_i$

Standard Population	Exposed	Unexposed
Total	$1 + \exp(-\hat{\lambda}' z_i)$	$1 + \exp(\hat{\lambda}' z_i)$
Exposed	1	$\exp(\hat{\lambda}' z_i)$
Unexposed	$\exp(-\hat{\lambda}' z_i)$	1

$\hat{\lambda}$ are corresponding maximum likelihood estimates to λ.

TABLE 7. Adjuvant Tamoxifen Use and Recurrence of Breast Cancer

	Exposed	Unexposed
Recurrence	464	424
Women-years	17228	17461
Estimated rate ratio = 1.11 (95% confidence interval = 0.97-1.27)		

in the estimation of propensity scores. Here we include a constant 1 in z_i so that the logistic model can contain the intercept.

Tamoxifen Use and Recurrence of Breast Cancer

Table 7 shows crude person-time data from an observational study of the effect of postoperative tamoxifen on the recurrence of breast cancer.[14] The study subjects were 6148 women who had been diagnosed with unilateral primary breast cancer and who had received surgical treatment between 1982 and 1990 at 9 institutions in Japan. The study was initiated in 1995 and the end of follow up was March 1996. Information on each patient was retrospectively obtained from medical records or a prospectively compiled computer database at each institution. Among 6148 women, information on recurrence was obtained for 4901 women shown in Table 7 as well as Table 2. The crude rate ratio was 1.11 with a 95% confidence interval of 0.97-1.27. There was no protective effect of adjuvant tamoxifen use on the recurrence of breast cancer. However, because the exposure to adjuvant tamoxifen use was not randomized, the crude results might have been confounded as in the previous risk-ratio analyses.

We conducted weighted Poisson regression analysis[1] in which the recurrence rate r was modeled as:

$$\log r = \omega_0 + \omega_1 e \quad (5)$$

with the estimated SMR weights $\hat{w}_{Ei}$ and where e is the exposure indicator (1, exposed to tamoxifen; 0, unexposed). The propensity score for each subject i was estimated by the

TABLE 8. Crude Data From the Pseudopopulation Created by the SMR Weighting

	Exposed	Unexposed
Recurrence	464	554.0
Women-years	17228	18303.6
Estimated rate ratio = 0.89 (Robust 95% confidence interval = 0.78-1.02)		

logistic model, providing the estimated SMR weights. We chose the following 4 covariates as confounding factors: age at surgery, stage of breast cancer, lymph node metastasis, and menopausal status. These variables were included in the logistic model. Table 8 shows the crude data from the pseudo-population created by the SMR weighting. The crude rate ratio in Table 8 is an unbiased estimate of the causal rate ratio, provided that there were no unmeasured confounders after controlling for these 4 covariates.

We can fit this weighted Poisson regression model using Proc Genmod in SAS (version 8.2, SAS Institute Inc, Cary, NC). The logarithm of each observed person-year is included as the offset variable in the option of "model" statement, and each estimated weight is specified in the "weight (or scwgt)" statement. The robust variance estimate can be obtained by specifying the "repeated" statement with the patient identification variable (ID) and the independent working correlation matrix ("repeated subject = ID/type = ind"). SAS code for the analysis of this example is given in Appendix 2. Estimated rate ratio was 0.89 with a robust 95% confidence interval of 0.78-1.02. Compared with the crude analysis given in Table 7, the adjusted analysis gave a remarkable to show the protective effect of adjuvant tamoxifen use.

In the calculation of a confidence interval, we used the robust variance estimate. It provides a conservative confidence interval for ω, which is guaranteed to cover the true ω at least 95% of the time in large samples.[10,15] In the weighted analysis, the fitted association models (2) or (5) assume risk or rate homogeneity within the same exposure subgroup. However, in the definition of the causal risk (rate) ratio, we need not assume such homogeneity. Thus, the variance functions of the fitted association models are misspecified, and hence the model-based variance estimate is not valid. For example, the variance estimate of log *SMR* from the stratified data given in Table 2 is 0.0034, whereas the model-based and the robust variance estimates of the SMR-weighted $\hat{\theta}_1$ are 0.0032 and 0.0037, respectively.

We conducted the usual Poisson regression analysis adjusted by the same 4 covariates. The estimated constant rate ratio is 0.87 with a 95% confidence interval of 0.77-1.00. Because possible effect–measure modification was anticipated, the interaction term between tamoxifen use and lymph node metastasis was added to the previous model. The estimated rate ratios with and without lymph node metastasis are 0.95 and 0.72; for the interaction term, $P = 0.06$. With this effect–measure modification, we need to have some population-averaged rate ratio estimator. The IPTW estimator proposed by Robins and colleagues[10,11] is one such measure when the target population is the total group, whereas the SMR-weighted estimator is also such a measure when the target population is the exposed subgroup.

Standardization using marginal structural models is based on differences in the baseline distribution of confounders. Therefore, it entirely avoids the problem, noted by Greenland,[16] of adjustment by person-time, which might be considered an outcome variable in the usual standardization approaches for stratified person-time data.

DISCUSSION

The marginal structural models with the inverse probability of treatment weights give the nonparametric multivariate extension of the standardization method with the total group as the standard population. We have shown that other choices of weights give the extension of the standardization method with other groups as the standard. All the weights can be calculated using the estimation of the propensity scores (Table 6). We primarily considered the estimation of ratio measures in the previous sections. It is straightforward to apply the proposed weights to the estimation of difference measures.[10] Marginal structural models with various sets of weights can be used as a useful tool for the standardization methods, depending on the appropriate choice of target population.

Appendix 1

Under the assumption of no unmeasured confounder, the counterfactual probability of any target population, $P(D = 1|\text{set } E = e, \textit{target population})$, is a weighted average of the stratum-specific risks with weights proportional to the distributions of Z in the target population;

$$P(D = 1|\text{set } E = e, \textit{target population}) = \sum_z P(D = 1|E = e, Z = z)\, P(Z = z|\textit{target population}),$$

where the sum is over the possible values of Z.[5] Simple algebra gives

$$\sum_z P(D = 1|E = e, Z = z)\, P(Z = z|\textit{target population})$$

$$= \sum_z \frac{P(D = 1|E = e, Z = z)}{P(E = e|Z = z)\, P(Z = z)} \times P(Z = z|\textit{target population})$$

$$= \sum_z \frac{P(D = 1, E = e, Z = z)}{P(E = e|Z = z)} \times \frac{P(Z = z|\textit{target population})}{P(Z = z)},$$

where $P(Z = z)$ is the distributions of Z in the entire study (total) population. The target population might sometimes be completely external.

When the total population is the target population, $P(Z = z|\textit{target population}) \equiv P(Z = z)$ and we have

$$P(D = 1|\text{set}E = e) = \sum_z \frac{P(D = 1,E = e,Z = z)}{P(E = e|Z = z)}.$$

This leads to the inverse probability of treatment weighting. Similarly, when the exposed group is the target population, $P(Z = z \mid \textit{target population}) \equiv P(Z = z|E = 1)$ and

$$P(D = 1|\text{set } E = e,E = 1) = \frac{1}{P(E = 1)} \sum_z P(D = 1,E = e,Z = z)\frac{P(E = 1|Z = z)}{P(E = e|Z = z)}.$$

The last term in the right-hand side is the SMR weights given in the text. When the unexposed group is the target population, $P(Z = z \mid \textit{target population}) \equiv P(Z = z|E = 0)$ and

$$P(D = 1|\text{set } E = e,E = 0) = \frac{1}{P(E = 0)} \sum_z P(D = 1,E = e,Z = z)\frac{P(E = 0|Z = z)}{P(E = e|Z = z)}.$$

Appendix 2

In this appendix, we provide SAS code to obtain the nonparametric multivariate extension of SMR described in the text. The following code is organized as follows. First, we use Proc Logistic to fit the logistic model in the estimation of propensity scores. Second, we use a SAS data step to calculate the proposed SMR weights for each subject from the estimated propensity scores of previous logistic model. Last, we use Proc Genmod to fit the weighted Poisson regression model that estimates the causal rate ratio.

The data file (SMR1) contains 1 record per woman. In the following code, the variable "ID" is the patient identification number and the variable "TAM" is a binary variable indicating whether a patient was exposed (TAM = 1) or unexposed (TAM = 0). The variables "AGE," "STAGE," "LYM," and "MENO" are age at surgery, stage of breast cancer, lymph node metastasis, and menopausal status, respectively. The variable "RECUR" is the binary outcome of recurrence. The variable "LOGPT" is the logarithm of observed person-times for each subject.

```
/* Estimation of Propensity Scores */
proc logistic data=SMR1;
  model TAM=AGE STAGE LYM MENO;
  output out=PRED p=P1;
run;
/* Calculation of the SMR weights */
data SMR2;
  set PRED;
  P0=1-P1;
  ODDS=P1/P0;
  if TAM=1 then WEIGHT=1;
    else WEIGHT=ODDS;
run;
/* Weighted analysis */
proc genmod data=SMR2;
  class ID;
  model RECUR=TAM
    /offset=LOGPT dist=poisson link=log;
  weight WEIGHT;
  repeated sub=ID / type=ind;
  estimate 'Beta' TAM 1 / exp;
run;
```

REFERENCES

1. Breslow NE, Day NE. *Statistical Methods in Cancer Research, vol II: The Design and Analysis of Cohort Studies*. New York: Oxford University Press; 1987.
2. Rothman KJ, Greenland S. *Modern Epidemiology*, 2nd Ed. Philadelphia: Lippincott-Raven; 1998.
3. Keiding N. The method of expected number of deaths, 1786-1886-1986. *Int Stat Rev*. 1987;55:1–20.
4. Miettinen OS. Components of the crude risk ratio. *Am J Epidemiol*. 1972;96:168–172.
5. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41–55.
6. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiologic confounding. *Int J Epidemiol*. 1986;15:412–418.
7. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995;82: 669–688.
8. Flanders WD, Rhodes PH. Large sample confidence intervals for regression standardized risks, risk ratios, and risk differences. *J Chron Dis*. 1987;40:697–704.
9. Greenland S. Estimating standardized parameters from generalized linear models. *Stat Med*. 1991;10:1069–1074.
10. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560.
11. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of the HIV-positive men. *Epidemiology*. 2000;11:561–570.
12. Joffe MM, Rosenbaum PR. Propensity scores. *Am J Epidemiol*. 1999; 150:327–333.
13. Greenland S. Interpretation and estimation of summary ratios under heterogeneity. *Stat Med*. 1982;1:217–227.
14. Matsuyama Y, Tominaga T, Nomura Y, et al. Second cancers after adjuvant tamoxifen therapy for breast cancer in Japan. *Ann Oncol*. 2000;11:1537–1543.
15. Robins JM. Marginal structural models versus structural nested models as tools for causal inference. In: Halloran E, Berry D, eds. *Statistical Models in Epidemiology*: *The Environment and Clinical Trials*. New York: Springer-Verlag1999:95–134
16. Greenland S. Absence of confounding does not correspond to collapsibility of the rate ratio or rate difference. *Epidemiology*. 1996;7:498–501.