

April 20, 2010

Dr. Suhair Shallal, Designated Federal Officer
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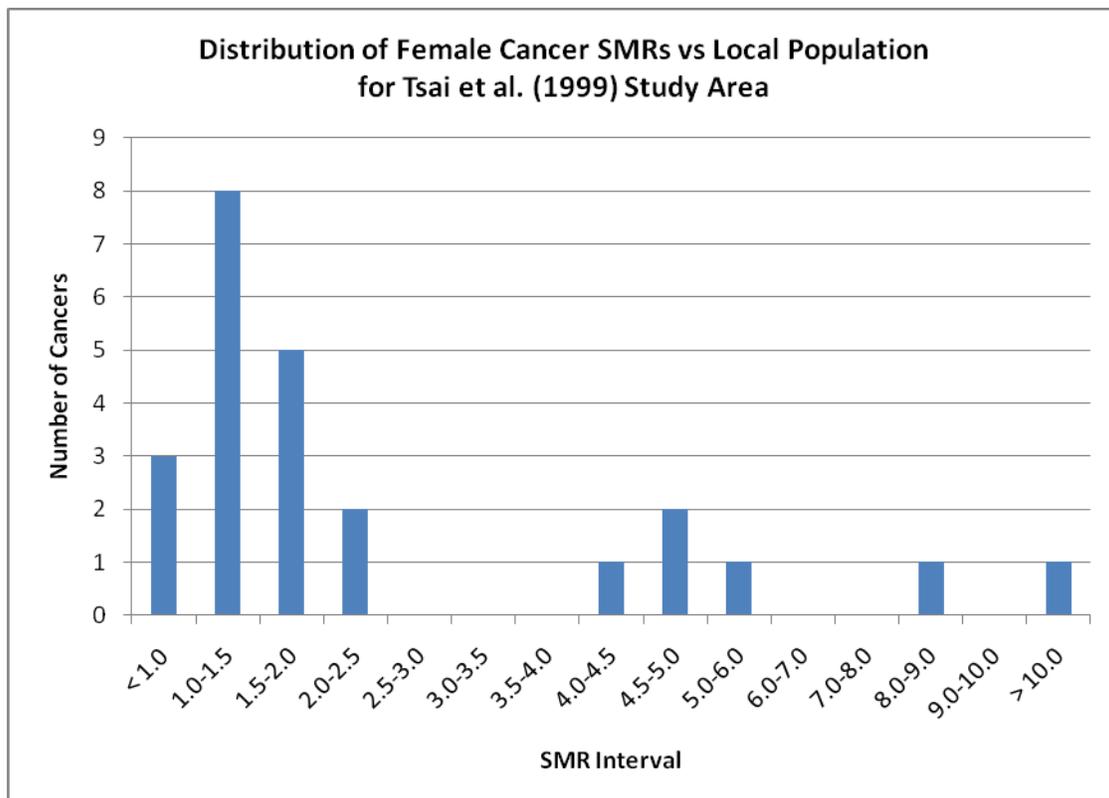
**Re: Tsai et al. (1999)
Female Cancer Mortality**

Dear Dr. Shallal,

An issue rose during the workgroup meeting as to whether mortality risks in the study area (Blackfoot disease endemic) were particularly elevated for bladder and lung cancer or generically elevated. We submitted to the work group the Tsai et al. (1999) paper from which we conclude that the answers to both questions are yes.

Tsai et al. (1999), in their epidemiological mortality study of the Blackfoot Disease endemic area (four primary townships of Peimen, Hsuechia, Putai, and Ichu), present standardized mortality ratios by sex using both a local reference group (Chiayi and Tainan counties) and the national reference group (i.e., Taiwan population) for the period 1971-1994. The SMRs for the two reference populations were quite similar. We shall discuss the analysis of the female cancer data vs the local population, as EPA considers females the more sensitive population and uses the local regional data as the reference group.

The figure shows a frequency distribution of the female cancer SMRs vs the local population (Tsai Table 3) [Appendix A]. The SMRs range between 0.9 and 14.1, suggesting a tri-modal distribution.



The two SMRs in the 8-14 range are the urinary tract cancers [kidney cancer (8.9) and bladder cancer (14.1)]. The four SMRs in the 4-6 range are the respiratory tract cancers [lung (4.1), laryngeal (4.8), and nasal (5.0)] and skin cancer (5.7). Categorically, these have been considered the “arsenical” cancers, though not laryngeal or nasal cancer.

The remaining 18 female cancer SMRs show a reasonably normal distribution with a median of 1.4 and do not have a body of literature supporting their being related to arsenic exposure. Fifteen of them (83%) have SMRs greater than 1.0, and half of them (9/18 = 50%) show a statistically significant increased risk. These are pharynx, stomach, colon, rectum, liver, bone, brain, cervix, and lymphoma.

Fifteen of the 24 female cancer SMRs (63%) are significantly elevated, and only six of those are in the cancer categories considered to be “arsenical.” Etiological factors for these additional cancers are not known.

Table 1
Standardized Mortality Rates for Female Cancers in Study Area vs Local Reference

<u>Cause</u>	<u>Observed</u>	<u>Expected</u>	<u>SMR</u>	<u>95% CL</u>
Cancer	2,029	843.9	2.40	(2.30-2.51)
Arsenical*	1,004	169.9	5.91	(5.54-6.28)
Other	1,025	674.0	1.52	(1.43-1.61)

* Respiratory, Skin, and Urinary Tract

The carcinogenic force for the “arsenical” cancers [SMR = 5.91; 95% CL, 5.54-6.28] seems to be of a different nature, possibly both quantitatively and qualitatively, than that for the other cancers [SMR = 1.52; 95% CL, 1.43-1.61] (Table 1). These analyses suggest that there is a general force of cancer mortality in the BFD-endemic area and a specific force of cancer mortality on arsenic-related cancers (urinary tract, dermal, and respiratory tract). The relative ratios (5.91/1.52 = 3.89) would suggest that a multiplicative carcinogenic force from arsenic would be about four-fold with respect to the background and general force.

In our accompanying analysis of the SW Taiwan cancer mortality, we have allowed for the possibility of a carcinogenic force not related to the arsenic level and included both an arsenic-level-related term (dose) and a non-arsenic-level-related term (ND) for the carcinogenic forces in the Blackfoot-disease endemic study villages.

Cordially,

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Appendix A

Female Cancer SMRs vs. Local Population (Tsai et al., 1999)

<u>Female Cancer Deaths</u>	<u>Obs</u>	<u>Exp</u>	<u>SMR</u>	<u>95% CL</u>
All Cancers	2029	843.90	2.40	(2.30-2.51)
<u>Oral and pharyngeal cancers</u>				
Oral	12	7.46	1.61	(0.83-2.81)
Pharyngeal	10	4.24	2.36	(1.13-4.34)
Nasopharyngeal	29	31.13	0.93	(0.92-1.97)
<u>Digestive system cancers</u>				
Esophagus	12	7.59	1.58	(0.82-2.76)
Stomach	111	79.46	1.40	(1.15-1.68)
Intestine	8	5.81	1.38	(0.59-2.72)
Colon	83	58.47	1.42	(1.13-1.76)
Rectum	33	21.98	1.50	(1.03-2.11)
Liver	224	119.28	1.88	(1.64-2.14)
Gallbladder	11	12.18	0.90	(0.45-1.62)
Pancreas	19	19.75	0.96	(0.58-1.50)
<u>Respiratory system cancers</u>				
Nasal	29	5.82	4.98	(3.33-7.15)
Laryngeal	13	2.73	4.76	(2.53-8.15)
Lung	471	114.02	4.13	(3.77-4.52)
<u>Other cancers</u>				
Bone	34	15.11	2.25	(1.56-3.14)
Skin	68	11.96	5.69	(4.41-7.21)
Brain	21	11.99	1.75	(1.08-2.68)
<u>Genital cancers</u>				
Breast	47	46.48	1.01	(0.74-1.34)
Cervical	122	96.09	1.27	(1.05-1.52)
Ovary	15	13.78	1.09	(0.61-1.80)
<u>Urinary tract cancers</u>				
Bladder	295	20.96	14.07	(12.51-15.78)
Kidney	128	14.40	8.89	(7.42-10.57)
<u>Lymphatic system cancers</u>				
Lymphoma	35	20.57	1.70	(1.18-2.37)
Leukemia	40	37.36	1.07	(0.76-1.46)

Bold = Statistically significant