

The Frequency of Multiple Primary Cancers: 1952-2004

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Objective: To evaluate the frequency rate and site of origin of multiple primary malignancies (MPM) in Bahrain from 1952 to 2004.

Design: Retrospective study.

Setting: Pathology Department, Salmaniya Medical Complex, Bahrain.

Method: Confirmed malignancies diagnosed in Bahraini patients from 1952 to 2004. The diagnoses are based on histopathology and hematology archives of the government, private hospitals and clinics.

Result: Six thousand nine hundred and nineteen cancer patients were found in the archives, 122 (1.7%) had MPM; 31 (25%) had synchronous and 91 (75%) had metachronous lesions, the annual frequency rate was 2.3 patients/year.

Equal M:F ratio was found, but males had more synchronous while females had more metachronous, double and triple cancers lesions. Sixty percent of all cancer patients were above the age of 50 years compared to 69% in all MPM patients, (74%) in synchronous, (67%) in first age metachronous and (77%) in second age metachronous lesions. The three most common metachronous MPM occurred in association with cancers of breast (21%), urinary tract (17%) and prostate (8%). Amongst males the commonest combinations occurred in association with cancers of urinary tract (28%), prostate (16.3%) and kidney (7%). Amongst female breast (38%), thyroid (10.4%) and urinary tract (6.3%) were the most common.

Conclusion: These results are reflection to the overall cancer pattern in Bahrain and may not apply to other regions or countries.

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The occurrence of multiple primary malignancies (MPM) of different histological types in

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the same patient; whether it occurred in the same organ or in different organs is rare and the frequency rate ranged at a misleading and disputable rate of 0.7% to 14.5%¹⁻⁸. The MPM could be synchronous, simultaneously discovered within the same year, or metachronously (successive) diagnosed thereafter.

The range of MPM is wide; therefore, we have embarked on an endeavor to establish an acceptable frequency rate of MPM based on the review of all microscopically confirmed archives of cancer patients diagnosed in the Arabian Gulf Kingdom of Bahrain from 1952 to 2004.

The aim of this study is to evaluate the frequency rate and site of origin of multiple primary malignancies (MPM) in Bahrain from 1952 to 2004.

METHOD

Histopathology and hematology archives of the government and private hospitals from 1952 to 2004 were examined. Standard criteria for recording the malignant lesion and MPM were used^{7,9}. These reports were analyzed for the number and annual frequency of patients with MPM, gender, age, date of diagnosis, anatomic site of origin, latency period and histological type of the tumors. The number of MPM occurring in each patient and the most common combinations were recorded. Latency period of MPM, refer to the time from the date of diagnosis of the first primary to the time of developing metachronous lesion.

The patients were grouped into two, those below the age of 50 years and those above. These two groups were studied for the frequency rates of cancers, including MPM, synchronous and metachronous cancers.

Furthermore, the following criteria were applied: (a) Patients with recorded age were included in the age analysis. (b) The age of patients with synchronous cancers was counted as one and assigned to their age groups. (c) First and second age of patients with metachronous cancer were counted to their corresponding age groups. (d) The first and second age of patients with triple cancer were counted to their corresponding age groups noting that those who had synchronous cancers were also counted as one. (e) The third age of patients with triple cancer was excluded from analysis.

RESULT

Table 1 shows the number, gender and age distribution of cancer patients diagnosed with MPM, synchronous and metachronous. Patients with synchronous lesions had double cancers while those with metachronous lesions 86 (94.5%) had double and 5 (5.5%) had triple cancers.

Six thousand six hundred and nineteen out of 6919 cancer patients had their age registered in the pathology archives. All the one hundred and twenty-two patients with MPM had their age registered.

Table 1: Number, Gender and Age Distribution of Cancer Patients Diagnosed with MPM, Synchronous and Metachronous

Characteristics	Results
Period of study	1952 – 2004
Total Number of Cancer Patients	6919 patients with 7146 malignancies 6630 with registered age 2671 (40%) below 50 years old 3959 (60%) above 50 years old
Patients with MPM (n=122)	1.7% of all cancer patients 117 (96%) double (234 malignancies) 5 (4%) triple (15 malignancies) lesions 249 MPM accounting for 3.5% all cancers 61 males (60 with double and 1 with triple lesions) 61 females (57 with double and 4 with triple lesions) 38 (31%) below 50 years old 84 (69%) above 50 years old
Synchronous Cancers (n=31 patients)	Account for 25% of all patients with MPM 18 (58%) males 13 (42%) females, M:F ratio 138:100 8 (26%) below 50 years old 23 (74%) above 50 years old
Metachronous Cancers (n=91 patients)	Account for 75% of all patients with MPM 86 (94.5%) patients with double cancer 42 (49%) males 44 (51%) females; M:F ratio 100:104 5 (5.5%) patients with triple cancers; one (20%) male 4 (80%) females, M:F ratio 100:400 43 (47%) males (42 with double and one with triple cancers) 48 (53%) females (44 with double and with 4 triple cancers) M:F ratio 100:111 Age distribution of first lesion: 30 (33%) patients below 50 years old 61 (67%) above 50 years old Distribution of second lesion: 21 (23%) and 70 (77%) patients respectively Of the 86 patients with double cancers 59 (69%) occurred within the first 5 years of first diagnosis, 22 (26%), 3 (3%) and 2 (2%) during the subsequent 10,15 and 20 years respectively

Table 2 shows the number and annual frequency rates of synchronous, metachronous and MPM. The annual frequency rate increased from zero between 1952 - 1964 to 0.3 between 1965 - 1974 and to 2.2 patients/year between 1975 - 1984. The rate between 1985 - 1994 and 1995 - 2004 remained at 4.8 patients/year. The overall annual rate was 2.3 patients/year.

Table 3 shows the number of patients with the three most common combinations of metachronous cancers. These lesions occurred in association with breast (C50), urinary tract (C65-C68) and prostatic (C61) cancers in 19 (21%), 15 (17%) and 7 (8%) patients respectively. Amongst males, they occurred in association with urinary tract, prostate and kidney (C64) cancers in 12 (28%), 7 (16.3%) and 3 (7%) patients. Amongst females they occurred in association with breast, thyroid (C73) and urinary tract cancers in 18 (38%), 5 (10.4%) and 3 (6.3%) patients respectively.

Table 2: The Number and Annual Frequency Rates of Synchronous, Metachronous and MPM

Period	Synchronous	Metachronous	All MPM	% of all MPM	Rate/year
1952-1964	None	None	None		
1965-1974	1	2	3	2.5	0.3
1975-1984	7	15	22	18.0	2.2
1985-1994	3	46	49	40.2	4.9
1995-2004	20	28	48	39.3	4.8
Total	31	91	122	100.0	2.3*

* The total rate /year correspond to the period between 1952 to 2004

Table 3: The Number of Patients with Three Most Common Combinations of Metachronous Cancers

First Cancer	Second Cancer
All MPM Patients	
Breast (C50) cancer (n=19)	3 hematological, 3 uterine, 2 ovarian, 2 thyroid, 2 urinary tract, 2 colorectal and one each with liver, renal, esophageal, cervical and nodal lymphoma
Urinary tract (C65-C68) cancer (n=15)	5 lung, 4 prostate, 2 uterine, and one each with rectal, esophageal, cervical and multiple myeloma
Prostate (C61) cancer (n=7)	2 renal, 2 urinary tract and one each with lung, colon and Chronic lymphatic leukemia
Males	
Urinary tract (C65- C68) cancer (n=12)	5 lung 4 prostate, one each with rectal, esophageal and multiple myeloma
Prostate (C61) cancer (n=7)	2 renal, 2 urinary tract and one each with lung, colon and Chronic lymphatic leukemia
Kidney (C64) cancer (n=3)	One each with larynx, oesophagus, stomach
Females	
Breast (C50) cancer (n=18)	3 hematological, 3 uterine, 2 ovarian, 2 thyroid, 2 urinary tract, and one each with rectal, liver, renal, esophageal, cervical and nodal Hodgkin's lymphoma
Thyroid (C73) cancer (n=5)	2 breast and one each with thymus, kidney, ovary
Urinary tract (C65-C68) cancer (n=3)	2 ovary and one cervix

The frequency associations of patients with breast cancer in the MPM group were similar to those found in the female list, the only difference being that of one male patient with breast spheroidal cell carcinoma and rectosigmoid adenocarcinoma. On the other hand, the frequency associations of patients with prostatic cancer in the all MPM group were similar to those in the male list.

Five patients in this series had triple cancer:

1. Fifty-four years old male had urethral (C68) squamous carcinoma and metachronous lung (C34) squamous cancer and urinary bladder (C67) transitional cell carcinoma diagnosed 4 and 9 years later respectively.
2. Sixty-three years old female had urinary (C67) transitional cell carcinoma and synchronous endometrial (C54) and colonic (C18) cancers developed 7 years later.
3. Forty-one year old female had breast (C50) lobular cancer and synchronous endometrial (C54) and colloid colonic (C18) cancers developed 6 years later.
4. Forty-five years old female had breast (C50) duct carcinoma and synchronous urinary (C67) transitional cell carcinoma and endometrial (C54) cancers diagnosed 4 years later.
5. Thirty-eight years old female had endocervical (C53) cancer and metachronous breast (C50) duct cancer and gastric (C16) cancer diagnosed 5 and 20 years later.

DISCUSSION

The frequency rate of MPM ranged between 0.7% and 14.5%^{1-6,8}. This wide range is misleading and questionable as no acceptable average rate can be quoted. There a number of factors responsible for this wide range including the following:

- The majority of published works on MPM are case reports which are difficult to assemble into a meaningful frequency rate^{8,10-12}.
- It is not clear in many studies whether the above range referred to the number of patients with MPM or MPM in studied series or it referred to synchronous, metachronous or both^{1,2,6,8,13}.
- Most reports lacked unified definition of MPM, synchronous and metachronous lesions; their inclusion criteria of cancer registration were variable^{4-6,13,14}.
- There are very few comprehensive clinical studies on MPM patients and these not only tended to have lower frequency rate, but also the majority lacked age, gender distribution, time of occurrence and commonest anatomic site^{3-6,8,10,12-17}. Few autopsy reports were mainly focusing on the number of MPM, which tend to have inflationary frequency rates because of the inclusion of incidental dormant microscopic foci of prostatic and thyroid^{2,6}. The type of hospital, method of autopsy and the selection of cases were found to influence the frequency rate^{1,2,6}.
- The rate at the lower end reflects not only the rarity of MPM but also the scarcity of recently published long term reports which can be used for comparative purposes^{1,2,4-6,12-14}.
- The rate at the upper end is influenced by reports based on risk factors and mathematical formulation of patients with specific primary cancer developing a second lesion elsewhere^{3-6,8,10-13,15-17}.

In present study, all of the above inconsistencies were addressed, namely it is a clinical study based on the review of all histopathology and hematology archives of cancer patients

diagnosed in Bahrain from 1952 to 2004; WHO criteria of cancer registration were applied. It also addressed the frequency of patients rather than frequencies of MPM. As such, patients with MPM accounted for 1.7% of all cancer patients while MPM accounted for 3.5% of all malignant neoplasm. It is hoped that this frequency rate of MPM patients, which is at the lower end of the above range should settle the ambiguities to establish a realistic rate of patients with these neoplasia¹⁻⁸.

MPM is increasing because of several factors mainly improved population age-related longevity rates, increased rate of early detection of cancer, greater awareness of the clinicians of the MPM problem, secondary effects of therapeutic cancer modalities, and the persistent effect of common etiology^{1,2,5,6,12,14,16}.

We found only two relevant studies which addressed the “increase issue” and both of these were post-mortem works; one by Parkash calculating an annual increase of 200/10,000 Viennese population and the other by Wanatabe et al from Japan estimating an increase of 10% of autopsy examinations/year^{1,2}.

The present study is based on review of histopathology archives; the annual increase was calculated in terms of number of patients with MPM per year, which is more acceptable than that per population or per numbers of biopsy material. Accordingly, progressive annual increase of MPM was noted from zero between 1952 - 1964 to 4.8 during 1995 - 2004. The average rate is 2.3 patients/year for the period between 1952 to 2004. Nonetheless, we believe that the rate of 4.8 patients/year calculated for the two successive periods between 1985 -1994 and 1995-2004 is the most likely annual increase rate of MPM because it remained static over 20 years period. However, this remained to be verified with future studies. Furthermore, it should be noted that these rates may be specific only to Bahrain and does not necessarily apply to other countries.

In MPM studies, patients with metachronous cancers were most commonly reported than those with the less frequent synchronous tumors^{6,11,14}. The frequency rates of these lesions in the present study were 75% and 25% respectively. Furthermore, most patients with synchronous or metachronous tumors had double lesions and patients with more than double cancers are even rarer appearing only as “case reports”^{1,2,6,11,14,15}. In the present study, 5 (4%) patients had triple cancers, all of whom had metachronous lesions.

Studies on latency period of MPM are mostly found in case reports. Long-term clinical studies are lacking. The relevant latency results of this study from Bahrain remain to be verified and compared with future studies from other centers. In the present study, 69% of the patients had their second cancer within the first 5 years of the first cancer and 26%, 3% and 2% during the subsequent 10, 15 and 20 years respectively. The rates may be specific to Bahrain only and does not necessarily apply to other countries because of population longevity rates, standard of healthcare reporting centre and the criteria applied for the cancer registration.

MPM is more commonly reported in male than female^{1,2,5,6,8,13,14,16,17}. However, in the present study the ratio was equal but with notable difference observed in patient with synchronous and metachronous double and triple cancers. Males had more synchronous cancers, the ratio was 138:100 while females had more metachronous, double and triple cancers, the ratios were 100:111, 100:104 and 100:400 respectively. Again, these ratios

may apply only to this study and appear to be influenced by the gender distribution pattern of cancer patients in Bahrain.

MPM patients tend to be older than those with single primary cancer^{1,6,13,14}. However, there are no universal criteria as to “when old age starts?” and to the definition of “living to extreme age”. Parkash studied 42,589 autopsy records and found 102 (0.2%) patients with MPM, 96% of these patients were above the age of 50 years and Demandante et al reviewed over 1.1 million cancer patients and found that 75% of those with MPM were above the age of 50 years^{1,6}. In both studies, the age distribution of all cancer patients was not provided for comparison of the two groups.

In this study, the age of 50 years was used to indicate “old age”. Accordingly, we noted that 69% of the MPM patients in Bahrain were above the age of 50 years and 74%, 67% and 77% of the patients with synchronous, first and second age metachronous lesions respectively were above that age. However, these results must be considered with caution since they may simply mirror the age distribution pattern of all cancer patients in the study rather than concluding that Bahraini cancer patients who are above the age of 50 years are at higher risk to develop MPM. Sixty percent of all cancer patients in Bahrain during the study period were above the age of 50 years⁹.

MPM occurrence in large cancer series, as in the present study, may indicate a reflection of the overall cancer pattern^{3-6,10,12,13,15-17}. The pattern of MPM combinations in China, Japan and Sweden are different from those of Bahrain^{2,5,14}.

CONCLUSION

In this study, patients with MPM were 1.7% of cancer patients in Bahrain; it is hoped that this rate should settle the varied ambiguities noted in the literatures. Differences of annual rate, age and gender distribution, latency period, and the occurrence of the most common metachronous combinations of MPM do exist. These differences appear to be a reflection of the overall cancer pattern in Bahrain and may not apply to other countries.

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