Table 39. Deaths among BCPT participants (Table 16, ERSMAC report)

Cause of Death	Placebo	Tamoxifen	Total
Cancer:			
Brain	3	1	4
Breast	5	3	8
Colon	1	1	2
Endometrial	1	0	1
Extrahepatic bile duct	1	0	1
Kidney	1	0	1
Lung	10	8	18
Lymphatic	4	1	5
Ovarian	1	2	3
Pancreas	6	2	8
Unknown primary	3	3	6
Thyroid	1	0	1
Vascular disease:			
Ischemic heart disease	8	7	15
Stroke	3	4	7
Other heart disease	4	5	9
Pulmonary embolism	0	2	2
Diseases of the arteries, arterioles, and capillaries	0	2	2
Other:			
MVA	2	0	2
Homicide	0	1	1
Nervous system disease	2	0	2
Non-infectious enteritis/colitis	1	0	1
Non-malignant respiratory disease	0	2	2
Pneumonia	0	1	1
Sarcoidosis	1	0	1
Septic shock	2	0	2
Systemic sclerosis	0	1	1
Surgical complications	0	1	1
Suicide	1	2	3

Unknown	4	4	8
Total	65	53	118

Reviewer Comment:

1. Case report forms for all participants who died were reviewed. The NSABP went to great lengths to accurately document cause of death. Documentation includes death certificates, hospital records, and physician notes and letters. There is extensive correspondence from the NSABP and local coordinators to state and county officials, hospitals, physicians, and family members in order to obtain these documents.

2. The following table is the reviewer's tabulations of cause of death. Differences from the sponsor's table are in bold print:

Table 40. Reviewer's Cause of Death

Cause of Death	Placebo	Tamoxifen	Total
Cancer:			
Brain	3	1	4
Breast	5	4	9
Colorectal	1	2	3
Endometrial	1	0	1
Extrahepatic bile duct	1	0	1
Kidney	1	0	1
Lung	10	8	18
Lymphoma/Leukemia	4	2	6
Ovarian	2	2	4
Pancreas	6	3	9
Unknown primary	3	2	5
Thyroid	1	0	1
Vascular disease:			
Cardiac/atherosclerotic disease	12	14	26
Stroke	3	4	7
Pulmonary embolism	0	3	3
Other:			
MVA	2	0	2
Homicide	0	1	1
Amyotrophic lateral sclerosis	2	0	2
Non-infectious enteritis/colitis	0	0	0
Non-malignant pulmonary fibrosis	0	1	1
Pneumonia	0	1*	1
Sarcoidosis	1	0	1
Septic shock	2	0	2
Systemic sclerosis	0	1	1
Surgical complications	1	0	1
Suicide	1	2	3
Unknown	3	2	5
Total	65	53	118

* In a participant with Parkinson's disease

Overall, there is general agreement between the reviewer and the NSABP. The reviewer collapsed ischemic heart disease, other heart disease, and diseases of the arteries, arterioles, and capillaries into one group because they are related and sometimes overlapping diseases. In addition, the distinction between these entities does not affect the major endpoints of this trial. Some cases were difficult to categorize precisely. For example, one participant died of complications from a CABG; this death could be categorized as ischemic heart disease or as complications of a surgical procedure. A

similar case involved a participant who died of a retroperitoneal bleed following an angioplasty procedure of the superficial femoral artery to relieve claudication. These types of cases account for most of the differences between the sponsor's table and the reviewer's table and are not discussed further.

Differences that involve major endpoints of the trial are discussed below.

Breast cancer versus CUP: Discrepancy on the tamoxifen arm

P45660LBM: see complete discussion of this participant in Section 9.1, Invasive breast cancer.

This patient was considered clinically by her treating physician to have metastatic breast cancer and was treated as such. She developed bony metastases and died of her disease 3/23/96. The death certificate recorded the cause of death as metastatic breast cancer. The NSABP coded it as unknown primary after several reviews. The reviewer considers this case to be consistent with metastatic breast cancer based on the mammogram reports, the prior diagnosis of LCIS, the receptor staining, and the judgement of the managing physician. This case was added to the number of invasive breast cancer cases diagnosed on study.

Pulmonary embolus versus non-malignant respiratory disease: Discrepancy on the tamoxifen arm

Participant P51364KEN was a 65 year old woman with the additional risk factor of a first-degree relative with breast cancer. She had a pre-existing biopsy-proven diagnosis of idiopathic pulmonary fibrosis in 1994 and began study drug 9/6/96. Because of increasing pulmonary problems, she discontinued study drug 3/4/97 and was treated with Imuran. She was admitted to the hospital 4/15/97 with pancytopenia and febrile neutropenia. A bone marrow biopsy showed hypocellularity but no malignancy. She received platelet and PRBC transfusions, leucovorin, and Neupogen in addition to broad-spectrum antibiotic coverage and improved. Her counts normalized and after a 10-day course of antibiotics, remained afebrile off all antibiotics for 4 days. She then acutely developed a fever, tachypnea, and a requirement for 50% oxygen supplementation. Previously she had not required any oxygen supplementation. Despite broad spectrum antibiotic and antifungal coverage, her lung function deteriorated. On 5/5/97, she was found pulseless and could not be resuscitated. The preliminary autopsy report showed pulmonary fibrosis and possible right pulmonary artery thrombosis, pending microscopic examination. The NSABP coded the cause of death as pulmonary fibrosis.

The reviewer noted the autopsy findings and requested the final report. The report noted a right pulmonary artery thromboembolus, with organizing microthrombi in smaller vessels. In addition, there was evidence of a transmural acute myocardial infarction, estimated to be between 3 and 10 days old. A small collection of malignant cells was found in one section taken from the right middle lobe. No site of origin was given. The reviewer classified this case as death from PE.

The sponsor agreed with the reviewer that the participant experienced a fatal pulmonary embolus as the cause of death.

Pancreatic cancer versus stroke: Discrepancy on the tamoxifen arm

PP16874UCL was a 66 year old woman with 2 first-degree relatives with breast cancer, s/p 4 breast biopsies. She had a history of hypertension and angina and was s/p angioplasty. She began study drug 10/26/93. On 11/29/94 she was diagnosed with pancreatic cancer and stopped study drug. A Whipple procedure was performed 12/14/94. In March 1995, she developed abdominal pain and was undergoing a work-up. She was treated in an ambulatory care facility 4/12/95 for pain. Chemotherapy was under consideration. On 4/17/95, her family called to report her sudden death at home, in the presence of family members. The NSABP coded her death as a stroke, as listed on her death certificate. While few details were available, the diagnosis of CVA as the preterminal event was apparently based on neurological signs described by the family—signs, which could have reflected brain metastases. Based on the available information, the reviewers (DG/SH) attributed the death to complications of her malignancy.

Stroke versus lung cancer: Discrepancy on the tamoxifen arm

P56876MSU was a 60 year old woman with a first-degree relative with breast cancer who began study drug 1/27/93. She discontinued medication on 4/15/95 because of concern regarding a persistent cough. She was subsequently diagnosed with lung cancer 8/24/95 that was metastatic to bone and liver. She was admitted to the hospital 9/8/95 with mental status changes, garbled speech, facial asymmetry, and left upper extremity paresis. A CT and MRI of the brain showed no evidence of cancer, but demonstrated multiple embolic phenomena with cortical edema of the right temporal lobe and left parieto-occipal junction, consistent with ischemia. A lumbar puncture showed a normal protein and glucose. She deteriorated clinically and expired 9/11/95. The physician who dictated the medical record listed embolic stroke as a diagnosis. The death certificate listed metastatic lung cancer as the cause of death. The NSABP did not list this event as a vascular death. Although the patient's underlying lung cancer was a contributing factor, the reviewers (DG/SH) attributed the acute event to a CVA.

3. These changes result in:

- A nearly equal number of breast cancer deaths on both arms, but the numbers are too low to draw any meaningful conclusions. At present, it is unknown whether tamoxifen can decrease the mortality rate from breast cancer.
- 3 documented deaths from pulmonary embolus in this trial, all on the tamoxifen arm. Overall, there is a 0.02% death rate from PE in NSABP P-1. Three of the 18 women who developed a PE on tamoxifen died from this event (17%).
- The number of fatal strokes on each arm did not change overall

4. There was one death from endometrial cancer in a placebo patient.

5. Deaths from other cancers and atherosclerotic disease were approximately equal on both arms. Overall, there was no difference in mortality between the placebo and the tamoxifen arms of the trial.

6. Deaths by center were also evaluated. One hundred thirty-four sites were designated for this study. Sixty-five centers had at least one death in a participant. The overall mortality rate for the trial was 118/13388 or 0.9%. At individual sites, the percentage of participants who died ranged from zero to 4%. This finding suggests that

some sites may not have considered competing medical problems when entering patients on study.

10.2 Endometrial cancer

Forty-seven cases of invasive endometrial cancer occurred, 14 on placebo and 33 on tamoxifen. Two cases of non-invasive endometrial cancer were reported, both on the placebo arm.

The annual hazard rates for invasive and in situ endometrial carcinoma are summarized in the following table:

Table 41. Average annual hazard rates of invasive and in situ endometrial cancer (Table 4, submitted P-1 manuscript)

Event	Number of Events		Rate/1000 Women*		Risk Ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Invasive	14	33	0.92	2.29	2.48	1.27-4.92
Age $\leq$ 49	8	7	1.19	1.11	0.94	0.28-2.89
Age $\geq$ 50	6	26	0.71	3.21	4.50	1.78-13.16
In situ	2	0	0.13	0	-	-

*Women at risk; non-hysterectomized

The sponsor states that there was no excess risk of endometrial cancer observed in women under age 50, and that the risk was confined to women over age 50.

The stage of the endometrial cancers as reported by the sponsor is as follows:

Table 42. Invasive Endometrial Cancers by FIGO stage

FIGO stage	Placebo		Tamoxifen	
	Number	Percent	Number	Percent
I	13	93	33	100
II and III	0	0	0	0
IV	1	7	0	0

Reviewer Comments

1. The CRFs for the 47 participants were reviewed by Alison Martin, M.D.

2. Median lengths of drug exposure and times to diagnoses were similar between the two arms.

3. Risk factors for endometrial cancer include obesity, the use of unopposed estrogen therapy, a background of hyperplasia, nulliparity/infertility, and medical

diagnoses of hypertension and diabetes mellitus. These factors for the women who developed endometrial cancer on study are summarized below.

Table 43. Risk factors in women diagnosed with endometrial cancer on NSABP P-1

Risk factor	Placebo (n=14)	Tamoxifen (n=33)	Total (n=47)
Weight:			
≤ 125	2	4	6
126-150	2	10	12
151-175	4	9	13
176-200	1	5	6
201-225	2	3	5
226-250	0	2	2
251-275	1	0	1
≥ 276	2	0	2
Past use of estrogen:			
No	10	21	31
Yes	4*	12**	16
Use of estrogen on study:			
No	13	29	42
Yes	1	4	5
Nulliparity:			
No	8	24	32
Yes	6	9	15
Hx diabetes mellitus			
No	13	33	46
Yes	1	0	1
Hx hypertension			
No	9	25	34
Yes	5	8	13

*All with progesterone use
**4 with estrogen use without progesterone

A higher number of women on tamoxifen were heavier, were more likely to have a prior history of unopposed estrogen use, to have used estrogen on study, have a history of hypertension, and to be nulliparous. However, most of the women on both arms of the study had few or no risk factors for endometrial cancer other than obesity, and these slight imbalances do not account for the excess number of cases observed on the tamoxifen arm.

3. Not all patients had signs or symptoms requiring evaluation according to review of the CRFs. Six women, 5 on tamoxifen and 1 on placebo, were asymptomatic.

The participant on placebo had a normal endometrial sampling performed 4/9/96 prior to her diagnosis of endometrial cancer 11/11/97. On tamoxifen, 1 participant had a normal sampling 8/6/96, before her diagnosis 8/29/97 at the time of her next scheduled sampling. Two women had hyperplasia diagnosed on screening approximately 2 months before the diagnosis of endometrial cancer. Two women had endometrial cancer diagnosed at their first endometrial sampling.

The use of clinical symptoms such as vaginal bleeding will probably not be sufficient to identify women at risk for endometrial cancer.

4. FIGO stage was verified by pathology report from the time of total hysterectomy in 46 of the 47 patients. The CRF on P46348BOS contains the pathology report from a biopsy for verification of the diagnosis; however, stage cannot be confirmed. The sponsor has been asked to supply the documentation for this case.

Reviewer Addendum:

The sponsor supplied the requested documentation 8/19/98; the participant was confirmed to have FIGO Stage IA endometrial cancer.

5. Some participants with FIGO IB endometrial cancer received postoperative radiation therapy, 6 on the tamoxifen arm and 1 on placebo, which may bear on risk/benefit decisions and survivorship issues of quality of life.

6. The sponsor has stated that the risk for endometrial cancer is confined to women aged 50 or greater. However, in this study, the expected pattern of an increase in cases of endometrial cancer in women $\geq$ 50 years of age (or women who are postmenopausal) compared to younger premenopausal women is not seen in the placebo arm. Of the 14 cases of endometrial cancer on placebo, 8 occurred in women under 50 years of age. If menopausal status at time of entry is substituted for age, the expected pattern is still not apparent with 10 of 14 women reporting menses at time of entry. The average annual hazard rate in women < 50 who received placebo was 1.19 (see Table 33), higher than the hazard rate based on SEER data for the general population or B-14 data. In the NSABP B-14 trial, the average annual hazard rates for the entire population were 0.2/1000 on placebo and 1.6/1000 on tamoxifen. The rates for women less than age 50 were 0 and 0.3 respectively. Thirty-one percent of the NSABP B-14 population was under age 50. The apparent increase in hazard rate for women < age 50 randomized to placebo in P-1 may be due to the high prevalence of risk factors common to both breast and endometrial cancer.

The tamoxifen arm in NSABP P-1 did not demonstrate a further increase in the risk of endometrial cancer in this prospectively defined subpopulation. However, the women on the placebo arm had a higher risk than that predicted by SEER data. It is difficult to assess whether there is no added risk of endometrial cancer from tamoxifen in young women, or whether an increased risk with tamoxifen (similar to that seen in B-14) was masked in this study by a control group with an unusually high rate of endometrial cancer.

7. These issues are summarized in the following table:

Table 44. Characteristics of participants diagnosed with invasive endometrial cancer[1]

Characteristic	Placebo N = 14	Tamoxifen N = 33[2]
Age at entry (yrs)		
Median	49	54
(range)		
Menopausal status at entry[3]		
Premenopausal	10	13
Postmenopausal	4	20
Age at randomization(yrs)		
<40	0	1
40 – 49	8	6
50 – 59	4	14
60 – 69	1	10
≥70	1	2
Age ≤ 49	8	7
Age ≥50	6	26
Time to diagnosis (mos)		
Median	31	30.1
(range)		
Time on study drug (mos)		
Median	27.9	27.8
(range)		
FIGO Stage		
I A	8	20[4]
B	5	12
C	--	1
II	--	--
III	--	--
IV	1	--
Postop radiation therapy	1[5]	5[5]
Suspicious signs/symptoms:		
No	1	5
Yes	13	28

[1]Adenocarcinoma, with the exception of one adenosarcoma with focal carcinosarcoma on the tamoxifen arm

[2]One patient randomized to tamoxifen never started treatment.

[3]As determined by patient questionnaire at entry.

[4] Coded as IA by NSABP. Pathology report absent from chart (see text above).

[5]All FIGO IB.

8. In summary:

- There were no characteristics other than tamoxifen use and obesity that predicted an increased incidence of uterine cancer
- Thirteen percent of women were asymptomatic and had normal prior endometrial samplings
- All except 1 of the endometrial cancers were Stage I. However, thirteen percent of women received radiation therapy in addition to a surgical procedure as definitive treatment.
- Tamoxifen did not increase the risk of endometrial cancer in women under age 50 in this study; however, the women under age 50 randomized to placebo had a risk higher than that predicted in the general population (SEER data) or in women with a prior diagnosis of breast cancer (B-14)

9. Two cases of non-invasive endometrial cancer were diagnosed, both on the placebo arm.

10. Information on other gynecologic problems was not systematically collected. During case report form review, the medical officers noted diagnoses of ovarian cysts in postmenopausal participants and endometrial polyps; in addition, there were notations of work-ups for dysfunctional uterine bleeding. Without a complete database, however, it is not possible to evaluate these events for a relationship to tamoxifen.

11. Endometrial sampling at baseline and annually was added as a protocol amendment. Four thousand three hundred forty-five women were screened from 1 to 5 times.

Of the 47 women who developed endometrial cancer, 26 had undergone at least 1 endometrial sampling. One comparison that could be made is shown below.

Table 44a. Endometrial Cancer Detection Rates (Per Patient)

Endometrial Cancer Status	Endometrial Sampling	No sampling
Number of Endometrial Cancers	26 (0.60%)	21 (0.5%)
Participants without Endometrial Cancer	4345	4182

The detection rate on a per patient basis (not per sampling) was significantly higher with endometrial sampling (Fisher's Exact Test, $p < 0.005$). Twelve women (0.28% of women with sampling) were found to have endometrial cancer only on sampling, 4 randomized to placebo and 8 randomized to tamoxifen. Six of these women (0.14% of women with sampling) had no antecedent signs or symptoms and diagnosis of their endometrial cancer might have otherwise been delayed. Four of the 6 were found to have endometrial cancer on routine sampling and the other 2 were found to have complex atypical hyperplasia, which was treated with hysterectomy and endometrial cancer was found incidentally during pathology review. Thus, sampling did not appear to significantly alter the detection rate for endometrial cancer.

10.3 Other cancers

One hundred seventy-three cases of cancer other than breast or endometrial were diagnosed. Eighty-eight occurred on placebo and 85 occurred on tamoxifen. The types of cancers (excluding breast and ovarian) are listed below:

Table 45. Confirmed number of invasive cancer events among BCPT participants (excluding breast and endometrium) (adapted from ERSMAC report, Table 13)

Cancer site	Placebo	Tamoxifen	Total
Buccal cavity, pharynx	0	2	2
Stomach	1	1	2
Colon	9	10	19
Rectum	3	4	7
Gall bladder	1	0	1
Pancreas	6	4	10
Larynx	1	1	2
Lung, trachea, bronchus	18	18	36
Connective tissue	2	0	2
Skin	9	10	19
Cervix	1	1	2
Ovary/fallopian tube	9	8	17
Other GU	2	3	5
Urinary bladder	1	1	2
Kidney	1	1	2
Nervous system	3	1	4
Endocrine glands	5	4	9
Lymphatic/hematopoietic	11	12	23
Unknown primary	5	4	9
Liver	0	0	0
TOTAL	88	85	173

In order to accurately capture information, the ICD-9 codes were used to classify events. No cases of esophageal, small intestine, other digestive organ, nose/sinus/middle ear, other internal organ, skeletal, eye, or ill-defined sites of cancer were identified.

Reviewer Comment:

1. In the course of reviewing the selected CRFs, the reviewers made notes of protocol events and compared the reports to the electronic database and to the sponsor's reports. The following skin cancers were noted in the CRF and are noted in the table above but were not reported in the electronic database:

Placebo:

P42868ELF Basal cell cancer nose, T1N0M0 6/20/94
P58494ARZ Squamous cell carcinoma in situ of the arm 10/9/92
P16563THM Basal cell cancer 1/24/94
P47311TOM Skin cancer, NOS 5/4/95
P58494ARZ SCCA in situ of forearm 10/9/92; placebo
P38166JSM 10/5/94 Oral lichen planus
P47522CIN 7/9/96 SCCA leg

Tamoxifen:

P27665SYR Basal cell carcinoma, 7/8/94
P30220PGH Well-differentiated SCCA arm, 9/14/93
P28162BCC Basal cell carcinoma, 5/96 and 7/7/96

During a meeting with the sponsor, the NSABP stated that skin cancers were excluded from their analyses. These cancers are not immediately life-threatening. The reviewer agrees with the sponsor's decision to exclude these cancers from the analysis.

2. Two cancers were recorded in the CRF but not in the database:

P52275JSM Polycythemia vera 11/9/94. Randomized to tamoxifen.
P29571BSF Myelodysplastic syndrome 4/10/97. Randomized to placebo

The NSABP indicated 9/23/98 that they routinely did not include these diseases in counts of invasive cancers. They will do so in the future.

3. Information on non-invasive endometrial cancer was collected, but data on non-invasive cervical cancer was not.

4. Overall, there is no difference in the occurrence of cancers other than breast and endometrium between treatment arms. Fornander and colleagues reported an excess risk of GI cancers associated with tamoxifen; no excess risk is seen in this large prospective randomized trial. Some investigators have reported an excess risk of ovarian cancer with tamoxifen administration; no such excess risk was observed in this study.

10.4 Cardiovascular events

A variety of cardiovascular events occurred on the trial and were summarized by the sponsor in the ERSMAC report:

Table 46. Cardiac and vascular events among BCPT participants (Table 14, ERSMAC report, volume 3, page 25

Types of events	Placebo	Tamoxifen	Total
Ischemic heart disease:	59	61	120
Fatal MI	8	7	15
Non-fatal MI	19	20	39
Angina w/ PTCA or CABG	12	12	24
Acute ischemic syndrome*	20	22	42
Other CV death	4	5	9
Other vascular:	80	111	191
Fatal stroke	3	4	7
Non-fatal stroke	21	30	51
TIA	21	18	39
Fatal PE	0	2	2
Non-fatal PE	6	15	21
Deep vein thrombosis w/o hospitalization	3	3	6
Deep vein thrombosis w/ hospitalization	16	27	43
Peripheral vascular disease	10	12	22
TOTAL	143	177	320

*New Q-wave on ECG but no angina or elevation of serum enzymes; or angina requiring hospitalization without PTCA or CABG

The reviewer discusses these events separately, categorized as cardiovascular events (MI, angina, acute ischemic syndrome, other CV death), stroke/TIA, peripheral vascular disease, and thromboembolic events (DVT, PE).

10.4.1 Ischemic heart disease

Ischemic heart disease was defined, in descending order of severity, as fatal myocardial infarction, non-fatal myocardial infarction, angina requiring angioplasty or coronary artery bypass graft, or acute ischemic syndrome. Participants who experienced more than one of these events were assigned to the worst category.

In the NSABP P-1 manuscript, a table of the annual hazard rates for ischemic heart disease was presented:

Table 47. Average annual hazard rates of ischemic heart disease (Table 6, submitted manuscript, P-1)

Event	Number of events		Rate/1000 women		Risk ratio	95% CI
	Placebo	Tamoxifen	Placebo	Tamoxifen		
MI:	27	27	1.13	1.13	1.00	0.57-1.78
Fatal	8	7	0.33	0.29	0.88	0.27-2.77
Non-fatal	19	20	0.79	0.84	1.06	0.54-2.09
Angina*	12	12	0.50	0.50	1.00	0.41-2.44
Acute ischemic syndrome#	20	22	0.84	0.92	1.11	0.58-2.13
TOTAL	59	61	2.47	2.57	1.04	0.71-1.51

*Requiring angioplasty or CABG
#New Q-wave on ECG; no angina or elevation of serum enzymes; no angina requiring hospitalization without surgery

There was no difference between treatment arms for any of these parameters.

Reviewer Comment:

1. Some of the events reported in Table 47 occurred after participants had discontinued study drug. These events are summarized below.

Table 48. Ischemic cardiac events that occurred after study drug was discontinued

Event	Placebo	Tamoxifen	Total
MI	6	4	10
Severe angina	4	3	7
Acute ischemic syndrome	4	3	7

The events occurred 1 month to 4 years after stopping study drug. If one excludes the events that occurred off study, the conclusions of the NSABP are not altered. Given that tamoxifen may have long-term effects on the incidence of cardiovascular disease, the reviewer agrees that all events that occurred in participants should be reported.

2. When the study was designed, the statisticians discussed the likelihood that participants would be at lower risk for cardiovascular disease than the general population. The risk factors for cardiovascular disease in the study population were examined using the electronic database tables submitted 7/31/98.

Risk factors in the entire study population:

a. Reported past cardiovascular events and baseline cardiac medications

A query of the database for pre-existing cardiovascular disease (past history of angina, heart attack, heart failure, heart murmur, transient ischemic attack, stroke, or

vascular problems) demonstrated that 1648 participants on placebo (25% of the treatment arm) and 1555 of participants on tamoxifen (23%) had a past history of one or more of the above events. Four hundred seventy-eight women on placebo (7%) and 949 on tamoxifen (14%) reported prior or current used of heart medications (exclusive of aspirin and antihypertensive therapy). These numbers are not balanced, but reflect a small part of the study population and probably had little impact on study results. Overall, few participants had had prior ischemic cardiac events, and few women required drug treatment of non-hypertensive cardiovascular problems.

b. Risk factors for ischemic heart disease

Risk factors for ischemic heart disease include a family history of cardiac events at a young age, tobacco use, hypercholesterolemia, diabetes mellitus, and hypertension. The distribution of these parameters is summarized in the following table: